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VASCULAR CONGESTION AND HYPEREMIA*

Their Effect on Structure and Function in the Female Reproductive System

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PART I. PHYSIOLOGIC BASIS AND HISTORY OF THE CONCEPT

Introduction

BESIDE the well-established organic lesions and certain disorders definitely attributable to endocrine dysfunction there still exists in gynecology a group of conditions of uncertain cause. These have the common characteristic of producing chronic pain without evidence of inflammation or other obvious pathologic process. They include the painful conditions of the breast commonly called chronic mastitis, the swollen, tender ovary usually designated "cystic," the enlarged, hypersecreting cervix, and the diffuse hypertrophy of the uterus, often termed "subinvolution."

These disorders have been known to many generations of gynecologists, but each has had a different concept of their nature. Thus, during the latter decades of the nineteenth century and up until about 1915 they were regarded as inflammatory, a view which has survived in a persistent terminology, notably

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in "chronic mastitis," "chronic metritis," "chronic cervicitis" and "cystic oophoritis." More recently, the knowledge of sex endocrine function has produced a new source of explanation of the unknown in gynecology and almost all nonorganic disorders, including those under consideration, are *ipso facto* regarded as "hormonal."

If progress is to be made, new factors in functional disorders must be considered. These are obviously to be looked for in disturbance of the autonomic nervous system and in associated abnormal vascular conditions. To consider these is in part to revive quite ancient ideas of pelvic pathology and in part to develop in gynecology the modern concepts of psychosomatic medicine.

A. The Hypothesis of Congestion and Hyperemia as a Source of Reproductive Tract Disorder

The material to be presented consists first of all in a consideration of some physiologic principles and then in a review and arrangement of the not inconsiderable mass of observations which has been published on this subject. This review will serve as an introduction to a series of 105 clinically studied cases. It may also lend needed support for what might otherwise appear to be a too abrupt change in the concept of the nature of many of the commonest gynecologic conditions.

The consideration of physiologic principles, the review of the literature and the analysis of the clinical case material will lead to four major theses:

1. The circulatory mechanisms of the reproductive tract are very labile and capable of rapid and extreme responses in terms of local intravascular blood volume as well as local extravascular fluid content, to hormonal, nervous, and other factors.
2. These changes in local vascular conditions are capable of causing pain, menstrual variations, and sometimes secretory disorders.
3. While such vascular changes usually chiefly affect one organ they are as a rule, to some extent, generalized throughout the reproductive tract, affecting uterus, adnexa, and breasts and may be regarded as a part of a single large disease entity or syndrome.
4. The effects of congestion, hyperemia and edema are at first temporary and reversible, but after these have persisted or been repeated over months or years permanent changes occur, chiefly in the form of hyperplasia of the connective tissues of the reproductive organs.

B. A Typical Case of the "Congestion-Fibrosis" Syndrome

Vivid descriptions of the disorder, or at least segments of it, are found repeatedly in the literature, but under a variety of titles, namely "pelvic congestion," "chronic parametritis," "subinvolution and congestion of the uterus," "hyperemia of the ovary," "sclero-cystic oophoritis" and "broad ligament neuritis." The entity under consideration is not, however, commonly accepted, at least in English-speaking countries; it is desirable, therefore, for the sake of orientation to give at the outset a general clinical picture. The following case is rather typical in illustrating most of the important manifestations.

CASE 27.—On March 8, 1937, this patient, a married woman of 38 years of age with two children, was first seen on account of suprapubic pain. She had been married for seventeen years, her younger child being eleven years old. Both children had been delivered without special difficulties.

Present Illness.—The present symptoms had appeared in a mild form many years before, but had increased markedly in the past year during a period of severe family tension.

The pain was chiefly suprapubic of variable intensity, worse before the menstrual periods and greatly increased by fatigue, the standing position, a family quarrel, and particularly by coitus. Dyspareunia was severe and frigidity had been complete since the first months of marriage. There was also premenstrual backache and occasional attacks of dysuria and urgency, the latter also since the early days of marriage.

The original menstrual periods had occurred every 28 days, lasted four days, were of average amount and without pain. Recently, although the cycle had remained the same, the amount of flow had decreased and lasted each month for only 1½ days and was preceded by severe back and suprapubic pain.

Leucorrhea of a mucous type had been present for many years, occasionally complicated by a little intermenstrual bleeding.

The breasts had developed a moderate tendency to premenstrual tenderness for several years before the first visit.

Beside the gynecologic symptoms, the patient suffered severely from insomnia and complained of dizziness, fatigue, and palpitation.

The Examination disclosed all of the signs typical of vasomotor disorder of the reproductive organs. The uterus was found retroplaced, but anteflexed, and at the first visit no enlargement was noted. The adnexa were tender but not notably increased in size. The cervix was greatly hypertrophied, slightly patulous, eroded moderately, with considerable fairly clear mucous discharge. The parametrium was very tender, as indicated particularly by the severe pain elicited when the uterus was gently elevated by the examining hand.

Course.—The patient was treated by cauterization of the cervix and by an attempt to obtain for her a quieter family life and a more relaxed outlook. There was some general improvement during the following seven years, but she was never well. The pain diminished but returned during any period of stress, notably when her son went into the army. The periods were quite variable as regards amount of flow and eventually became intermittent. The dyspareunia and frigidity remained unchanged. Attacks of dysuria occurred on several occasions.

Operation.—In November of 1942, pain developed in the right side and the possibility of an acute appendicitis could not be excluded in spite of a normal sedimentation rate and blood count. At operation there was found no evidence of any acute inflammation or of any previous salpingo-oophoritis. The peritoneum of the pelvis appeared slightly edematous and there were about 50 c.c. of clear amber fluid in the cul-de-sac. The uterine fundus was found to be about twice normal size, soft and bluish, with slight descensus. The cervix was still eroded. The tubes were edematous and hyperemic, apparently patent, with a few fine adhesions. The ovaries were normal in size, fibrotic and a little cystic with a fresh corpus luteum on the right side.

The operation consisted of a dilatation and curettage, a cauterization of the cervix, a round ligament suspension, a right salpingo-oophorectomy and an appendectomy. The pathology report showed: "Secretory endometrium; follicular cysts of the ovary; normal appendix."

During the three years since the operation the picture has changed little. Pain and tenderness have disappeared from the right side but there are occasional attacks of left-sided pain, involving at times the left breast, left abdomen, and left leg. With the approach of the menopause there have been occasional periods of amenorrhea during which time all pelvic symptoms are better.

This case has been presented as a typical, although severe example of the disorder under discussion. It illustrates for each part of the reproductive tract,

the characteristic symptoms and the clinically observable pathologic results of what appears to be a vascular and autonomic nervous-system disorder.

C. The Physiologic Control of Reproductive Tract Circulation

The pelvic circulation has certain characteristics of structure and of function which make it susceptible to disturbances of a special sort. Some of these peculiarities are found in the breast as well.

Four separate factors, acting alone or in various combinations, may be responsible for changes in the pelvic circulation. These are fundamentals that must have preliminary consideration (Table I).

TABLE I. FACTORS AFFECTING PELVIC CIRCULATION

Mechanical	Gravity and posture Fascial support Rectal and sigmoid function
Inflammatory	Hyperemia of acute inflammation Permanent vascular injury
Estrogens	Hyperemia Fluid retention
Nervous stimuli	Specific local stimuli Specific general stimuli Nonspecific nervous states

1. The Effect of Mechanical Factors, Including Gravity.—The anatomic characteristics of the veins are the source of many of the peculiarities of the pelvic circulation and of the disorders arising in it. These veins are said to be unusually dilatable, deficient in valves, with a relatively weak attachment between adventitia and the surrounding connective tissue support.[67, 79] The volume of blood contained in the veins of the pelvis is unusually large in relation to that of the arteries (Cotte[20]).

The absence of valves and the weakness of the vein walls is probably responsible for the development of varices in the broad ligament, comparable with those of the hemorrhoidal veins. In spite of a large literature,[44, 30, 80, 90, 23] the occurrence of clinically significant varicosities of the broad ligament has remained debatable. This uncertainty is probably due to the fact that the veins of the broad ligament are subject to examination only at operation with the patient in a horizontal position when collapse of the veins occurs. The development of a dilated venous system, with or without varicosities, may well be a contributing factor in the production of local circulatory disorders. It occurs especially in women whose pelvic veins are constitutionally defective (Auvray[3]) and in those whose pelvic supporting tissues have been weakened by childbirth.

A point emphasized by some writers[32, 44] is the greater frequency of pain and ovarian enlargement on the left side. This has been attributed to the special anatomy of the left ovarian vein which enters the renal vein at an acute angle, unguarded by a valve, whereas the right vein enters the vena cava obliquely, its entrance covered by a perfect valve (Tait).[96]

Another feature of importance in the pelvic venous system is the rich anastamosis with the vesical and hemorrhoidal vessels. This produces the tendency for disorders, originating in any one of the three pelvic organ systems to have effects on the circulation of the other two also. Bladder and rectal symptoms are of some frequency in cases of pelvic congestion and constipation has been regarded as affecting the entire pelvic circulation.

The importance of the venous system of the pelvis in determining gynecologic symptomatology can scarcely be overestimated. Although recent anatomic studies have emphasized the behaviour of the coiled arteries on the initiation of menstruation, it is chiefly from the veins that the bleeding comes.[25, 64, 65] The amount of blood lost and to some extent the duration of flow is therefore chiefly dependent on the conditions prevailing in the pelvic venous system and upon factors, such as myometrial tone, which control venous bleeding.

Because of the position of the pelvic veins at the lower end of a column of blood reaching to the heart, gravity plays an important part in determining conditions within the pelvic circulation. The venous pressure in the pelvis undoubtedly varies greatly with the position of the patient. This fact is most spectacularly demonstrated by the immediately favorable effect of the recumbent position on excessive uterine bleeding.

The effect of a raised venous pressure in the pelvis on the transudation of fluid from the capillaries into the interstitial tissues of the pelvis has been discussed particularly by Derichsweiler[26] in relation to "edema of the endometrium." This in an exaggerated form is probably the cause of the edematous swelling of uterus, cervix, ovaries and subperitoneal tissues, as well as the slight increase in free intraperitoneal fluid, sometimes observed in the cases under discussion.

That gravity plays a small part in the symptoms of the painful types of chronic mastitis is also evident. Especially with premenstrual engorgement in the large and pendulous breast, adequate support gives considerable relief.

The mechanism of the effects of uterine malposition on local circulation is not entirely clear, although it appears certain that major degrees of retroversion and all degrees of prolapse may be associated with stasis or congestion. This may be due to simple loss of support for the thin pelvic veins, resulting from the weakening of fasciae and ligaments, possibly to a twisting or kinking of the veins causing some venous obstruction.

2. The Effect of Inflammation.—Inflammation in the pelvis certainly often plays a role in the production of temporary local hyperemia. It is indeed often impossible to distinguish between a primary inflammatory condition of the cervix and one superimposed upon a state of chronic vascular congestion.

There may also be permanent effects on the pelvic circulation of an acute or subacute bacterial parametritis, for it is difficult to explain the persistence of pelvic symptoms years after a miscarriage or abortion otherwise than on the basis of permanent damage to veins or lymphatics.

3. The Effect of the Estrogens.—The circulation of the reproductive organs has the special quality of being affected by the estrogens and perhaps by other steroid hormones. Here the effect is perhaps mainly arterial and the results should properly be called a hyperemia rather than a congestion, although the effect of an increased arterial inflow would certainly be to add to any congestion already present. The vascular effects of the hormones are apparent to any clinician in the change in appearance of the genital mucosae and areolae before menstruation, in early pregnancy, and following the administration of the estrogen to women in the menopause. The effects in the laboratory are evident in such experiments as those showing the reddening of the rat or mouse uterus a few hours after estrogen injection, in the capillary changes in rabbit endometrium transplanted to the anterior chamber of the eye.[71, 72] In a recent report, Loeser[69] has also demonstrated the vascular reactions of the human endometrium to estrogenic injections.

A storage of salts and fluid in the interstitial spaces with a consequent swelling of the tissues is a constant phenomenon of estrogen administration. This has been shown for the rat uterus where it was noted that the enlargement for the

first twenty-four hours was not accompanied by any increase in protein content, but only by an increase in fluids and electrolytes.[2, 97] Such an increase is indicated in blood and interstitial fluid by the extraordinary swelling of the sexual skin in some primates.

Retention of fluid is also well known to occur in women before menstruation. That this is in part generalized throughout the body is probable, but the evident swelling of the breasts and the premenstrual sense of congestion in the pelvis makes it almost certain that a considerable part of the retained water is held specifically in the tissues of the reproductive organs.

The excessive retention of fluid in the cases of so-called "menstrual edema"[103] and in "premenstrual tension" or "distress"[42, 59] are of great interest in this respect, because many of the symptoms described for the latter condition are found also in the patients of the present series. That the estrogens are the cause of premenstrual tension has been alleged[5, 41] but the evidence to show that excessive estrogens are present in these cases is inconclusive.

The estrogens and perhaps other steroids are thus important factors in maintaining pelvic blood supply and the fluid and electrolyte content of the tissues. The estrogens are furthermore responsible for the normal premenstrual increase in pelvic blood supply and tissue fluids. That in excess they may produce excessive vascular effects is only a possibility.

4. The Effect of the Autonomic Nervous System.—The circulation of the female pelvic organs is likewise beyond doubt controlled to a large extent by the pelvic autonomic nervous system. The reproductive organs are, as is well known, supplied by sympathetic fibers, through the ovarian and hypogastric plexuses and by parasympathetic fibers, through the pelvic nerve arising from the sacral segments of the cord. These autonomic nerves are concerned largely with smooth-muscle and blood-vessel tone and have only an indirect relationship with endocrine function and the sexual cycle. In general, the parasympathetic causes vasodilatation of the vessels of the female genitals and inhibition of the musculature, the sympathetic producing the opposite effects.[107]

Vasodilatation may apparently be produced by three types of stimuli:

(a) Local sensory stimuli received in the external genitals will be carried by afferent sympathetic fibers in the pudendal nerve, mediated in sacral and lumbar centers, returned peripherally through the parasympathetic fibers of the pelvic nerve to cause vasodilatation throughout the reproductive tract.

(b) Psychic stimuli of a specific sexual character having varied sensual origins may, after undergoing complicated conscious and subconscious modifications, also obviously produce pelvic vasodilatation.

(c) Psychic stimuli of a nonsexual character presumably also affect the circulation of the pelvis. The relationship of nonsexual emotions, such as worry, anxiety, fear, and tension, to disorders of the pelvic circulation have remained almost unconsidered, but clinical evidence suggests that these nonspecific emotions have their profound effects on the autonomic nervous system here as elsewhere in the body. Nervous tension has, for instance, been observed to produce in different patients of the series to be presented sudden swelling of the breasts, uterine cramps, backache, and mucous discharge from the cervix. The relationship between chronic vasodilatation and prolonged emotional states is still less readily demonstrated but forms the subject matter of a later section of this article.

The effect of the autonomic nervous system on the pelvic circulation can of course not be seen in isolation or separated completely from endocrine and particularly ovarian function. The cervical ganglion of Frankenhauser has been

studied and found to undergo morphologic alterations in relation to available estrogen. The cells of the ganglion suffer degenerative changes when the animal is castrated or its ovaries radiated and there is regeneration when such castrated animals are treated by ovarian extracts.[6, 7, 8, 9, 66]

The factors which affect blood supply in the pelvis are, then, the special anatomy of the veins, gravity and other mechanical factors; the history of past or existence of present inflammation; the steroid hormones, and the autonomic nervous system. These, either singly or in combination, are capable of producing rapid as well as profound chronic alternations in local vascular conditions. That disturbances in an apparatus so delicate should be common and productive of numerous symptoms is at once probable.

D. The Concept of a Congestion-Fibrosis Syndrome in the Reproductive Organs as Derived From Previous Work

Many observations have already been made on what may be called the "Congestion-Fibrosis Syndrome" in the female reproductive organs. The work on this subject has, however, never been assembled since it is listed under a great variety of titles as well as being scattered through the literature of several countries.

The first step must be the collection of this material, its analysis, and the formulation of some underlying principles. It is indeed necessary to note for each segment of the reproductive tract the evidence for a clinical disorder based on congestion, for the later development of fibrosis, and for the association of these conditions in the organ under consideration with the same disorder in other parts of the reproductive tract.

1. The Mammary Gland.—Since changes in the breast are most easily observed and also because infection as a cause may be excluded with the utmost certainty, this organ forms a useful starting point. The subject in relation to the breast has furthermore already been considered in detail by this writer in a series of papers on the etiology of chronic mastitis.[98, 99, 100, 101, 102]

In these articles on chronic mastitis, the conclusion was reached[99, 101, 102] that there probably existed two forms of diffuse breast disease, one characterized by premenstrual pain and swelling and by a diffuse, nodular induration, the other by a secretion of a milky or oily discharge from the nipple. The former, in a broad sense, was regarded as having prominent neurovascular aspects, the latter being perhaps chiefly endocrine in origin.

The former type for which the name adenofibrosis was used, belongs in the present category of reproductive tract disorders. Two phases in the development of adenofibrosis were recognized; one of disturbed function characterized by premenstrual engorgement and swelling and the other of organic change, characterized by fibrosis.

The circulatory factor in the typical premenstrual swelling of the breasts seems evident. The alternative view that the enlargement is due to an epithelial cycle in the mammary gland is quite untenable on account of the rapidity of the development of the swelling and its still more rapid disappearance after the onset of each monthly period. Histologic evidence of a peracinar edema is found in some breast sections and seems to be most pronounced in tissue obtained during the premenstruum.[99, 29] The importance of a vascular factor in adenofibrosis has been in general accepted in a recent review by Nathanson.[108]

The almost invariable presence of nodular induration of the breast tissues in cases with a history of prolonged and excessive premenstrual engorgement is

the evidence associating the two processes of congestion and fibrosis. Tissue removed from breasts of this clinical type in the later stage is noted on gross section to have a shining, white, smooth texture and on histologic study is found to consist chiefly of fibrous tissue. The extensive literature on the role of fibrosis in the pathogenesis of chronic mastitis has been reviewed by Taylor and Waltman.[102]

In the series of 261 cases of chronic mastitis, evidence was found of several associated gynecologic conditions that at first appeared to be quite heterogeneous and unrelated.[99, 100, 101] A considerable number of patients reported scant or diminishing menstruation,[101] a point commented on by at least six previous writers on chronic mastitis.[98] An apparently large group had suffered from, or been operated on for "cystic ovaries."[99] Physical examination showed "cervicitis" in one-half of all of the cases and in one-fourth a marked tenderness in the broad ligaments. This tenderness of the parametrium was observed and recorded before the writer had any knowledge of the German literature of "chronic parametritis" or of the French concept of "chronic pelvic congestion."

Patients with this type of breast disease have often been regarded as of a special nervous disposition, and believed to suffer from a variety of associated complaints apparently arising in other organs. Their pain often takes the form of an hyperesthesia of the overlying skin and frequently radiates to parts well beyond the breast itself. The literature on these neurotic or psychiatric aspects of breast disease has also been previously reviewed.[98]

2. The Uterus.—In considering the pelvic lesion resulting from vascular disorder, the French have devoted most of their attention to the uterus itself, the Germans to the parametrium. Study of the descriptions found in the literature, however, strongly suggests that the French *congestion uterine* and the German *parametritis chronica* are identical.

The descriptions of Aran[1] (1858) are referred to by several of the modern French writers as the beginning of the concept of uterine congestion as a definite entity, but numerous earlier writers, including some English gynecologists, were evidently familiar with the clinical aspects of the disease (Gooch,[51] Churchill).[13] Aran's views were stated before the advent of bacteriology and his concepts were soon superseded by the idea of infection. Uterine congestion became "chronic metritis." Toward the turn of the century it became evident, however, that the bacterial origin of many uterine conditions could not be demonstrated and the idea of symptoms and signs resulting from uterine congestion was revived in French gynecology at least.[92, 81, 82, 83, 84]

At present, uterine congestion seems firmly established in France and forms a definite chapter in modern French works on gynecology.[34, 35, 32, 20, 14] According to these French writers, the uterus in this condition is enlarged, soft, and deep red in color. The patient suffers from lower abdominal and lower back pain of characteristic location and radiation and from disturbances in the menstrual flow. The case for uterine congestion is stated less definitely in the literature of other countries, but is evident in the work of several writers.[28, 54, 47, 48, 87, 70, 60]

The evidence for the congestion has depended largely on the clinical and gross pathologic findings, which are, however, striking enough. Derichsweiler[26] alone has made an attempt to catch the fleeting circulatory changes under the microscope in a paper on the "Edema of the Endometrium." In his study he noted edema and overfilling of the vessels of the mucosa, the former of which he ascribed to filtration processes resulting from changes in the hydrostatic pressure in the blood stream of the pelvis and the latter to an increased inflow or obstructed outflow of blood.

The uterus of pelvic congestion is manifestly temporarily enlarged but some gynecologists go further and maintain that as a result of connective tissue

proliferation the enlargement becomes permanent and a condition of hypertrophy results. The direct relationship between the congested and the enlarged fibrotic uterus is maintained by a group of French writers[92, 82, 83, 20, 34, 35, 32, 33, 14] but is also suggested by some Germans[88] and Americans.[49, 54] To this group there probably belong the not inconsiderable number of cases formerly termed "chronic metritis" or "parenchymatous hypertrophy" and now usually "diffuse hypertrophy" or "subinvolution."

That the congestion is not strictly localized to the fundus is recognized by all writers who give this point any consideration. Cotte states rather categorically that the phrase "uterine congestion" is a misnomer, and that on account of the richness of the anastamosis of the uterine vessels, particularly the veins, with those of the entire genital tract, including the ovaries and even rectum and bladder, it is difficult to recognize a local condition. This is an important point.

Associated signs of congestion in other parts of the gynecologic area have been often noted. Mucous leucorrhea is almost always present[20, 34, 35, 32, 26, 87, 60, 54] and the cervix has been described as having a turgid, violaceous appearance.[32, 33] An association with congested and eventually fibrotic or cystic ovaries is described by others and is apparently widely accepted.[20, 32 33, 49, 60, 27] The participation of the pelvic cellular tissues in a tissue edema is suggested by Cotte[20] indicating a transition to the German concept of chronic parametritis.

In cases of uterine or pelvic congestion, as in cases of adenofibrosis of the breast, there is usually an associated psychological disturbance. This manifests itself in depression, anxiety, or irritability and not infrequently in psychosomatic symptoms referable to the cardiovascular or gastrointestinal tracts.[5, 14, 32, 20]

Fig. 1.—Hypertrophied, congested uterus in comparison with normal nulliparous uterus.

The characteristics of the hypertrophied congested uterus are shown in Fig. 1, in which a normal, nulliparous uterus from a woman in the same age group is placed for comparison. The removal of this hypertrophied uterus was indicated for persistent dysmenorrhea, lower abdominal pain, backache, and retroversion in a woman in her early forties. The hypertrophy was associated with the characteristic softening and cyanotic coloring seen in these cases.

3. The Cervix.—Cervical signs or symptoms have been described by many writers as a part of pelvic congestion, these descriptions coinciding closely with the common picture of "chronic cervicitis." The almost universal observation

of leucorrhea as a symptom of pelvic congestion has been noted.[20, 34, 35, 32, 33, 26 89, 60, 54, 91, 76, 48] Other writers have described the cervix of pelvic congestion as swollen and edematous, violaceous or deep red in color.[54, 32, 48] They have noted the enlargement, the boggy consistency, the patulous external os,[34, 35] the swelling of the mucosa, the hypersecretion of the glands and the erosion.[60] The symptoms ascribed to congestion of the cervix include beside the leucorrhea, lower abdominal and back pain, and sometimes dysmenorrhea and menorrhagia.

The common hypertrophy of the cervix, the presumptive late stage of cervical congestion, seems to have evoked extraordinarily little enquiry as to its causation. The occurrence of this hypertrophy in cases of malposition, particularly of prolapse, is at least suggestive that the congestion resulting from gravity or the weakening of the support of the pelvic veins has been an important factor in producing connective tissue proliferation. An enlargement of the cervix has been noted by some writers as an accompaniment or late result of pelvic congestion of other origin.[60, 34, 35]

That congestion of the cervix accompanies signs of a similar process in other parts of the reproductive tract has been indicated already. Noteworthy are the reported associations of cervical signs or symptoms with uterine congestion, with "chronic parametritis,"[47, 48, 62, 56] with cystic ovaries,[94, 73] and with chronic mastitis.[99]

Inflammation evidently plays an important part in the clinical conditions described and in part justifies the universal designation of "chronic cervicitis." The remaining question is whether this infection, as manifested by the mucopurulent type of discharge and the presence of leucocytes in the stroma of the cervix, is primary or secondary.

The symptoms and signs of pelvic congestion have been perfectly described by several writers who have ascribed them entirely to the effects of cervicitis and lymphatic drainage to the parametrium.[94, 56] Graefe[55] refers "chronic parametritis" to chronic cervicitis. Young[104, 105] describes a similar condition under the term "cervical syndrome" and reports a high percentage of cures with the cautery. On the other hand, Hyams[57] clearly recognizes a special category of cases due to "circulatory stasis" and both he and Goodall[52] warn that conization or the cautery are liable to result in failure in this group.

There appears to be no doubt that following a gonococcal infection and in the badly lacerated cervix a chronic nonspecific inflammation may be the principal factor, either through its direct production of symptoms or through its contribution to the pelvic hyperemia. For the anatomically normal cervix, however, the primary condition is perhaps usually a general pelvic congestion, which, by causing a hypersecretion of mucus and dilatation of the canal, results in erosion and a susceptibility to mild superficial secondary infection.

4. The Parametrium.—In the German literature, a gynecologic disorder with clinical characteristics identical with those noted for chronic pelvic congestion has been described as "chronic parametritis." With this difference in anatomic area of principal interest, there was also a tendency in the German school to stress the late results, namely the fibrous bands and contracting scar tissue developing in the parametrium and particularly in the uterosacral ligaments.

The first formal description of "posterior parametritis" was published in 1876 by Schultze, who recognized an earlier "inflammatory phase" and later phases of fixation and malposition of the uterus as a result of contracting scar tissue. There followed, in 1885, the work of W. A. Freund[47] which in the opinion of this reviewer still represents the classical clinical description of the disease. In a series of subsequent articles appearing over the next fifty years chiefly in German but partly in the American literature, the existence of this

entity, usually termed chronic posterior parametritis, has been repeatedly confirmed by able clinical observers.

Although the fibrosis of the uterosacral ligaments remained the point of chief interest, the idea of a preliminary "active" phase of congestion or inflammation has been repeatedly advanced. This early stage of congestion or inflammation is clearly stated in the articles of W. A. Freund[47, 48] of Ludwig Fränkel,[39] of Ziegenspeck,[106] and Kehrer.[62] The edema of the pelvic tissues is referred to briefly by the French writers, Molin and Condamin,[77] and by Cotte. American writers have, although less definitely, indicated their belief in a circulatory engorgement leading to fibrosis in the broad or uterosacral ligaments.[49, 58, 74]

The resulting fibrotic changes have, however, received the most attention. The gross anatomy of the abnormal connective tissue bands was examined in some detail and both diffuse and circumscribed forms recognized and the localization of special bands described.[48, 106] Correlations of clinical observations obtained from the examination of moribund patients on a general hospital ward were made with later autopsy dissections.[106] Histologic studies were also made and reported to show rarefaction of muscle bundles, swelling of connective tissue, and decrease of elastic fibers, sclerosis of vascular walls, dilatation of the blood vessels in the early stages, and reduction in the number and size of the vessels in the later stages of the disease.[39, 47, 48, 10]

The exact nature of the process going on in these ligaments has remained open to dispute. Although the terminology of inflammation has been continually used, the concept of inflammation was never defined in bacteriologic terms and it seems probable that the inflammation of the Germans is the equivalent of the congestion of the French. For the later stages the majority has been satisfied that the process was chiefly fibrosis.[106, 47, 48, 91, 10, 11, 62] A small group have, however, maintained that a contributing factor was a spastic contraction of the ligaments due to an "overexcitability of the smooth muscle of the female sex organs."[78, 4, 86, 92]

Of particular interest, in view of the symptoms and signs of autonomic nervous system disorders in these cases, are the reports of damage to the pelvic nerves. Freund[47, 48] described a proliferative perineuritis ("neuritis prolifera") of Frankenhauser's ganglion with separation of the cells by new connective tissue, degeneration of the nerve fibers and eventual disappearance of the ganglion cells. H. W. Freund[43] also reported changes in Frankenhauser's ganglion consisting in edema, cellular infiltration, proliferation of connective tissue and pigmentary atrophy of the ganglionic cells. Cotte[20] derives a group of symptoms which he terms "hypogastric plexalgia" from these lesions which he identifies with those of the chronic parametritis of the German writers. In a study made with Dechaume,[22] he describes the histologic lesions of the hypogastric plexus found in cases of this type as including congestion, microscopic hemorrhage, edematous distention of the perineural sheath and sclerosis of the nerve. They suggest three stages in the process, vasodilatation, serous exudation, and sclerosis. Implications of nerve involvment are also made by two modern British gynecologists who after describing conditions similar to the above quite frankly use the term, "broad ligament neuritis" (Young,[105] Sutherland[95]). Although some of these observations are very old ones and none may be said to be controlled by adequate pathologic or experimental study, they are highly suggestive and offer a basis for many of the physical aspects of this disease.

With this so-called "chronic parametritis," signs of involvement of other organs of the genital system have frequently been reported. The uterus is noted as large, especially in the early stage.[48, 27] There is hypersecretion of the cervix.[48, 62, 45] The ovaries may be swollen and tender or in the later stages

small and firm.[48, 39, 21, 27] Of special interest is W. A. Freund's observation[48] of associated tender nodules in the breasts. The congestion and fibrosis of the parametrium is thus just a part of a process affecting the whole reproductive tract. In many cases the principal manifestations are actually in this area, while in others the exclusive localization in the uterosacrals is the result of the bias of the particular observer.

Finally, as in the case of "chronic mastitis" and "uterine congestion," general nervous instability of the patient is emphasized by many writers. Freund,[48] for example, entitled his paper "Uber die durch Parametritis chronica atrophicans hervogerufene Hysterie." Schultze[91] noted "hysterical" symptoms in 15 of his 21 cases. Fränkel,[39] Kehrer,[62] and to a less extent others note the accompanying nervous and emotional manifestations.

5. The Ovaries.—The tender enlarged ovaries found in young women with recurrent lower abdominal pain are common problems in gynecologic practice. The pain, though intermittent, tends constantly to return and leads often to an abdominal operation when an ovary which appears almost normal is removed, often with only incomplete relief of the pelvic pain. These ovaries were at one time regarded as "prolapsed" and are now usually termed "cystic." The basic pathology and the cause of the pain remain largely undetermined.

There has existed, however, for many years a theory, comparable to those offered for the breast, uterus, and parametrium, that the ovary is subject to pathologic degrees of chronic congestion, that the persistence of this leads to the proliferation of new connective tissue in the cortex and that this fibrosis finally produces an obstacle to ovulation. There then develops as a consequence multiple follicular "retention" cysts.

The history of this theory has followed somewhat that of "the congestion-fibrosis" syndrome in the other parts of the reproductive tract with thinking confused by the constant intrusion of concepts of inflammation and the inability to bring under the microscope the transitory signs of vascular disorder. To begin with a classical work, one finds in Lawson Tait's[96] *Diseases of the Ovaries*, published in 1883, a clear recognition of ovarian hyperemia as a symptom-giving condition which when it lasts too long or becomes too severe leads to "chronic ovaritis" with enlargement and later atrophy. Subsequently, many writers have referred, often somewhat vaguely, to hyperemia as a contributing cause.[73, 12, 75, 40, 89, 50] Today the concept of the "cystic ovary" as the result of vascular congestion appears most completely accepted by the French gynecologists.[33, 35, 36, 14]

The congestion is, however, only the beginning of a complicated process, for, when this is continued for a long time, fibrosis occurs causing interference with ovulation and small cyst formation.[94, 36, 18, 14, 47, 48] Other writers have noted comparable regressive changes in the ovaries as a result of varicocele of the broad ligament.[31, 3] For the end result of this process, the French use the precisely descriptive term "sclerocystic ovaries." Histologic studies have been made of the sclerocystic ovary, indicating not only fibrosis but complex, proliferative regeneration of sympathetic nerve fibers, even minute "neuromas" which have been regarded as the basis for the pain and sensitivity of this condition.[85, 68]

The subject has recently been complicated by the advent of the endocrine factor as a possible cause, the multiple cysts being regarded as the result of excessive anterior pituitary stimulation. The ripening of follicles as a result of gonadotropic hormones has become a laboratory commonplace and cystic changes in the ovaries of women previously injected with gonadotropes have been observed in the course of surgical operations. Nevertheless, it is quite uncertain that the tender, swollen ovary so commonly observed by the clinician has such a cause. Indeed, it appears probable that two or more types of condition are

covered by the clinical term "cystic ovary," one painless and perhaps endocrine in origin, the other painful and belonging to the category of lesions being discussed in this paper.

References to the association of the cystic ovary with other manifestations of the congestion-fibrosis syndrome in the same patient have already been noted, namely with chronic mastitis[99, 100, 101]; with uterine congestion[70, 61, 62, 21, 49, 33]; with cervical congestion[73, 94]; and with chronic parametritis.[48, 39, 21]

Manifestations of nervous irritability are commonly reported in women with sclerocystic ovaries. Thus, one finds references to excessive impressionability, exaggerated nervous reactions, disseminated neuralgic pains, associated migraine and indigestion, and other symptoms resulting from disordered autonomic function. In respect to these associated nervous phenomena, the cystic ovary also resembles its possibly analagous conditions already described in uterus, parametrium, and breasts.

The problem of the painful fibrocystic ovary is illustrated in a recent case, not one of the present series, from which Figs. 2 and 3 were obtained.

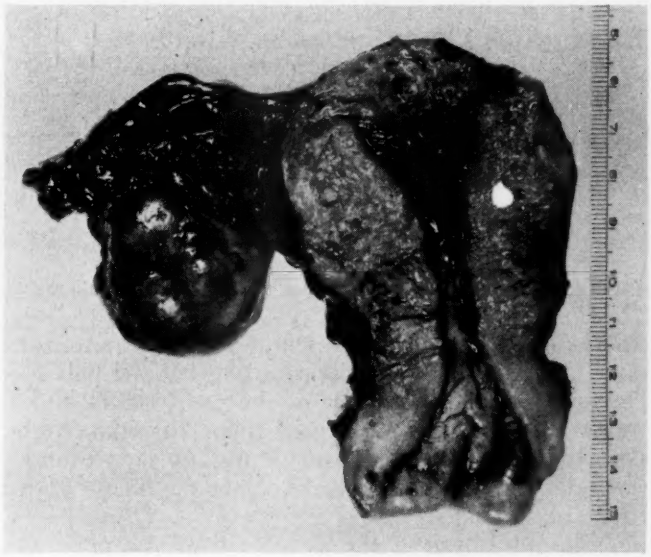

Fig. 2.—Uterus and ovary of patient with chronic pelvic pain.

CASE A. G.—This patient was first seen in the admitting department of the Vanderbilt Clinic on Oct. 13, 1939, at the age of 25 years, when a diagnosis of chronic pelvic inflammatory disease was made. Her past history included two spontaneous but difficult deliveries, an appendectomy, and a removal of the left tube and ovary for a "cyst."

She remained under observation in the clinics of the hospital for eight years. During this time she was treated for fainting attacks, nausea, vomiting, epigastric pain, colitis, dysmenorrhea, menorrhagia, insomnia, a nervous breakdown, premenstrual tension and at one time a suspected thyrotoxicosis. She has in her record twelve emergency visits to the dispensary for abdominal pain, one admission to the medical ward, and three to the gynecologic service. In spite of all this, she had a third normal pregnancy with a spontaneous delivery at the Sloane Hospital in October, 1944.

She was under almost constant social service supervision for her difficult home conditions and received some formal psychiatric advice for "anxiety neurosis."

As a result of persistent, intractable right-sided pelvic pain, dysmenorrhea, and dyspareunia, she was finally treated on her third gynecologic admission by total hysterectomy and a right salpingo-oophorectomy, performed on April 1, 1948.

The uterus (Fig. 2) was a little large. The ovary was twice normal size, rounded in shape with the embossed surface resulting from small underlying cysts. On section (Fig. 3) the ovary was found to be made up of multiple follicular cysts.

The case is typical of the course and pathologic findings of many cases of this type.

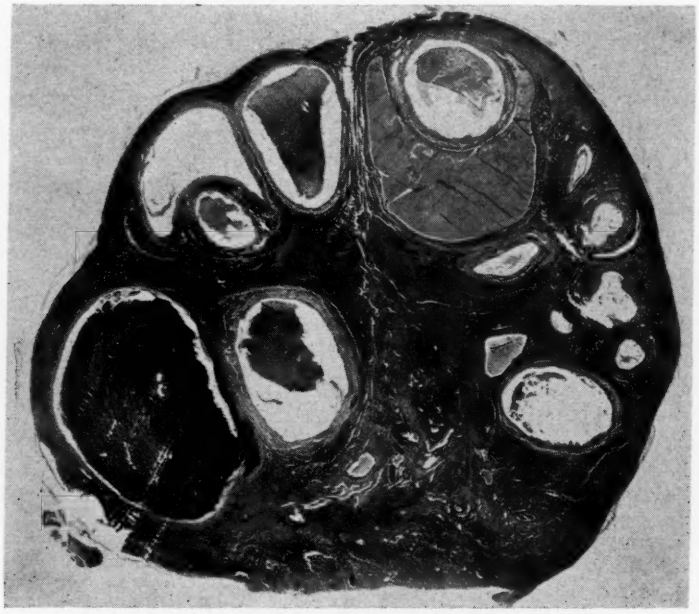

Fig. 3.—Microscopic section of ovary associated with chronic pelvic pain.

6. The Peritoneum.—That the peritoneum and subperitoneal areolar tissues of the pelvis should partake of the effects of a generalized pelvic congestion is to be expected. The edematous appearance of the peritoneum and the presence of some fluid was noted in the preliminary case report in this article. Goodall and Power[54] have described similar conditions found at laparotomy and Crossen[24] describes what he calls "fulminating pelvic edema." These observers have each suggested an allergy as the cause.

As a perhaps chronic phase of this condition of the peritoneum, Condamin describes what he terms "douglasitis." There can be little doubt from the characteristics of this disorder as presented by Condamin[15, 16, 17, 18, 19] that it is a part of the process called pelvic congestion in its early phases, chronic parametritis in its later.

Summary of Concept of Congestion-Fibrosis Syndrome as Derived From a Review of the Literature

The review of the literature interpreted with regard to what is known of pelvic vascular physiology has led to the description of what may be called the congestion-fibrosis syndrome. The fundamental processes concerned are given in outline form in Table II.

About the congestion-fibrosis syndrome, the following may be said in summary.

1. Each part of the reproductive tract is subject to characteristic disturbances in vascular function, manifesting themselves in the form of arterial

dilatation, venous engorgement, and probably local increases in extravascular tissue fluids. This vascular disorder results in pain in the breasts, ovaries, and parametrium, hypersecretion from the cervix, and menstrual anomalies.

2. For each organ of the reproductive tract, independent observers have believed that there could be distinguished an early congestion phase leading to a later one of fibrous tissue proliferation. That such a pathologic process should result under conditions of prolonged vascular stasis is entirely possible.

3. Since manifestations of the congestion-fibrosis syndrome in one segment of the reproductive tract are commonly found associated with signs and symptoms of the disorder elsewhere, this process must be regarded as one which is often generalized throughout the reproductive system.

4. Patients having symptoms of genital tract congestion are found characteristically to suffer from emotional instability, radiating neuralgic pains, and symptoms such as palpitation and indigestion. These associated nervous phenomena indicate a strong autonomic factor in the syndrome.

TABLE II. THE CONGESTION-FIBROSIS SYNDROME

	CONGESTION STAGE	FIBROSIS STAGE
Uterus	Uterine congestion	Diffuse hypertrophy
Cervix	Hypersecretion Endocervicitis and erosion	Hypertrophy
Parametrium	General pelvic congestion	"Chronic posterior parametritis"
Peritoneum	Edema Increased ascitic fluid	"Douglasitis"
Ovary	Congestion	Fibrocystic ovary
Breast	Premenstrual engorgement Mastodynia	Chronic (fibrous) mastitis

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(Parts II and III of this presentation will appear in subsequent issues.)

Discussion

DR. W. C. DANFORTH, Evanston, Ill.—In directing our attention to the congestion-fibrosis syndrome, Dr. Taylor brings to our attention a condition which bulked far larger in the minds of gynecologists of a generation ago than in those of the last twenty-five years. Perhaps, in our interest in the highly developed technical side of our work, and the perhaps overemphasized interest in endocrine therapy, we have lost sight of something which should not have been allowed to escape us and perhaps the skepticism with which some present-day gynecologists may be inclined to greet the subject may not be wholly justified. In the few days which have elapsed since the full manuscript reached me I have not been able to spend sufficient time in the library to go over the large number of authors whom he quotes. These are chiefly French and German with some American and English. Prior to receiving his paper, however, I obtained the book of Gustave Cotte, written in 1928, entitled, *The Functional Disturbances of the Female Reproductive System.* (Les Troubles Fonctionnels de l'Appareil genital de la Femme.) In this volume is found a chapter devoted to a discussion of congestion of the pelvic organs. This seemed to be a real clinical entity to the author. He states that for normal function an integrity of the vessels which make up the pelvic circulatory system is needed. He believed that, with normal vessels, the sympathetic system would not be able to provoke sudden vasomotor change. In addition to physical or nervous strain there must be, therefore, some deterioration in the pelvic vascular system. He also referred to the glands of internal secretion but a discussion of their function nearly thirty years old would not be of great value today.

His arrangements of cases into groups resembles considerably that of Dr. Taylor. He describes passive congestion, produced by long hours of standing, long automobile journeys, or protracted work at the sewing machine, or by disorders of the circulatory system, especially decompensation of the heart. Disease of the liver or kidneys may also be a cause.

Primary congestion, still quoting this author, may be found at all periods of life and he discusses the symptoms in young girls, menstruating women, and in women past the menopause. He believed that long-continued stasis might produce what some authors refer to as subinvolution and that some of these patients might ultimately sink into neurasthenia or melancholy. The large, rather symmetric uterus, with a greatly increased production of fibrous and elastic tissue, has recently been referred to as "hypertrophy."

Cotte states that the symptoms may vary rapidly from day to day, apparently not being dependent upon structural changes in the pelvic organs, particularly in patients in whom the condition has not lasted long enough to produce structural changes. The symptoms he enumerates are essentially the same as those of which Dr. Taylor speaks. A sense of weight in the pelvis, tension, heat, and irritation especially toward the vagina and anus. He emphasizes the turgescence of the vulva which he refers to as purplish (violacée). Some patients may find it difficult to walk or even to sit. Leucorrhea may be increased in amount. He quotes a Spanish author (Castanro) as having found varicose masses laterally to the uterus but states that he has not observed this. The uterosacral ligaments may be tender. Disorder of other systems may be present, as enterocolitis, migraine, and asthmatic attacks.

Psychic disturbance may be a cause. This is emphasized both by Cotte and by the essayist. I recently saw a woman who might well be included in this category. About 42 years old, she complained of pelvic pain, backache, and tenderness was elicited on both sides of the pelvis. No abnormality of any sort was found on examination. She had two aged and infirm parents in her home, whose demands upon her, both physically and nervously, were extreme. I had not read Cotte's book at the time but my advice to her was that no active therapy was needed but that relief from family strain, long hours of rest at night, and a few naps in the afternoon would probably cure her.

As one goes through Dr. Taylor's paper one meets a few old friends of the examining room. These are the tender ovary, especially in young women, and tender breasts without any sign of growth. I am sure that most of us have saved women from ill-advised operations for such things without ourselves being able to do as much for the patients as we would like. The term "mastitis" has always troubled me, for it is a poorly descriptive word except as applied to infection, usually during the puerperium. If Dr. Taylor can help us with these two things alone he will have performed a service.

The essayist's conservative attitude toward surgery is to be commended. Probably far too many operations are done for conditions of this sort and the essayist's experience seems to indicate that many of them are unsatisfactory.

Dr. Taylor has at least given us something to think about. The French School seems already rather well convinced of the reality of the existence of the congestion-fibrosis syndrome. Our own clinical experience of the next few years will enable us to determine its position in American gynecology.

DR. EDWARD A. SCHUMANN, Philadelphia, Pa.—Dr. Taylor's fascinating paper will carry us all back some sixty or seventy years and recall the congestive syndromes described by Dr. Taylor and Dr. Danforth as recorded by the late gynecologists of the nineteenth century.

I am in complete agreement with almost everything Dr. Taylor has said regarding this congestion syndrome and would like to point out that the many patients who apply to gynecologists are often cured by suggestive therapy, kindly advice, and consequently require no further treatment. When the condition continues for a length of time it becomes irreversible.

Dr. Taylor speaks of the phase of congestion and the phase of fibrosis with no intervening period. We use the term inflammation rather loosely because, as I understand it, it is a reaction of tissue to trauma, so that the trauma, causing engorgement and emptying of

the vessels, the excitation of the lymph tracts that discharge the lymph, is sufficient to produce inflammation without an infection. This may readily proceed to a true fibrosis which is described by the essayist.

I tend to discredit the endocrine factor in producing this congestion syndrome. It is interesting to note that while the older literature was scattered, that is due simply to the fact that each man wrote upon the subject that he was engaged in studying at the moment. To Dr. Taylor we owe the whole putting together of this syndrome, except that he left out the headache and the indigestion, which is probably also due to the same cause.

Lastly, I should like to point out that while the essayist has noted that major surgery is much decried, in Dr. Taylor's whole series of patients but one was classified as completely cured and that was by hysterectomy.

DR. WILLARD R. COOKE, Galveston, Texas.—We should be grateful to Dr. Taylor for reviving a concept of real importance which, as we all know, has more or less lapsed from our gynecologic consciousness. My own interest dates to the early years of association with a Chief who, as was customary in those days, operated on all cases of retroversion. In attempting to find out why the majority of these patients had no symptoms, I finally became convinced, to a reasonable degree of certainty, that the symptomatology varied directly with the degree of congestion and the resultant changes in the tissues drained by the veins involved. Later, a correlation was established between congestion originating in the genitals and symptoms referable to adjacent viscera. The best example in this group is the vesical symptomatology so frequently seen in connection with fibromyomas and commonly attributed to "pressure" of a nodule upon the bladder. Almost unbelievable distention of the bladder commonly occurs without vesical symptomatology: whereas the entire subjective symptomatology may be referred to the bladder in cases of very small nodules contiguous to it. Cystoscopy discovered that the vesical symptomatology was in direct proportion to capillary and venous engorgement in the wall of the bladder, not always contiguous to the fibromyoma. Still later, a relationship between genital congestion and symptomatology, and dysfunction and disease primary in adjacent viscera was reasonably established, the most familiar example being in cases of the spastic colon-colitis sequence. Finally, circulatory disturbances due to endocrine and psychic factors were subjected to study.

In regard to the tissue changes brought about by long-maintained congestion, we are in full accord with Dr. Taylor, very definitely so in the case of fibrosis of the ovary. We feel that the concept of "replacement fibrosis," long held in contempt by pathologists, should be revived. We are less certain as to the uterus, because of the extreme variability of the histologic characteristics in the enlarged uteri which he describes. In fact, we are so much at sea that in our laboratory we call them merely "big uteri." I must confess that we have never attempted to correlate genital congestion with coccydynia.

From the clinical aspect, especially in private practice, we have found that the commonest cause of pelvic congestion and its sequelae lies most often in the spastic colon-colitis sequence; next in the sedentary life, the most spectacular cases being seen in the high school athlete who is suddenly transferred to the physical inertia of the life of the typist, the telephone operator, or the wife of a well-to-do husband. Next in some order come the cases of physical genital disease, of suppressed or frustrated libido, and of many other abnormalities.

Altogether, the concept of circulatory disturbances is one which deserves further recognition and investigation.

DR. LUDWIG A. EMGE, San Francisco, Calif.—In connection with Dr. Taylor's interesting discussion of vascular disturbances of the female reproductive organs, I like to present a vascular disturbance of the uterus infrequently met with. Cavernous hemangioma of the myometrium, as far as I know, has not been diagnosed preoperatively probably because the symptomatology simulates uterine adenomyosis. The rarity of the condition is evidenced by the fact that in our extensive pathologic material only three instances of hemangioma of the uterus have been encountered. The specimen presented here is the most typical seen by me.

(Figs. 1 and 2.) In this case a mass of hemangiomatous channels pervades all of the myometrium. In two other instances the hemangioma was found only in the lower third of the corpus. In each case the uterine veins were huge and tortuous. I have no way of telling in what way the two conditions are linked. However, the presence of huge pelvic varicosities involving mainly the uterine circulation and the progressive intensification of pelvic symptoms over a period of years hints at an acquired factor. We expect to describe this condition in greater detail in the near future.

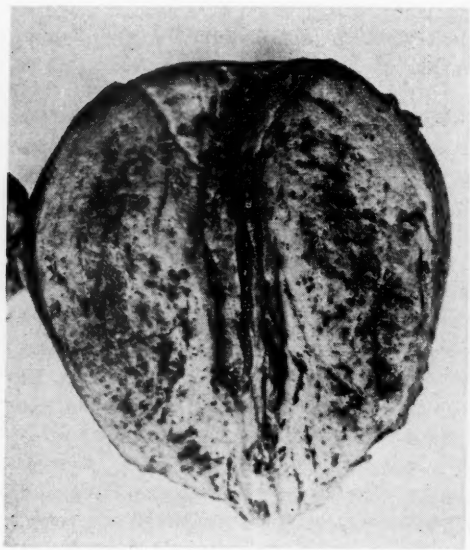

Fig. 1.

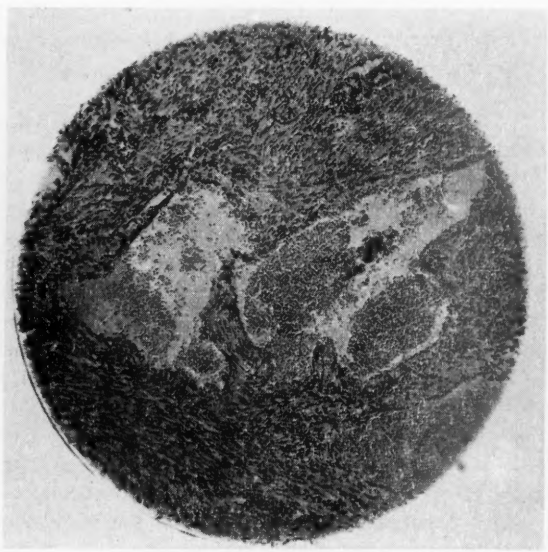

Fig. 2.

Fig. 1.—Corpus Uteri, 10 by 7 by 7 cm. Progressive severe dysmenorrhea and menorrhagia. Nullipara, aged 35 years. Preoperative diagnosis: adenomyosis.

Fig. 2.—Cavernous intercommunicating bloodspaces lined with a single layer of endothelial cells permeate the entire myometrium.

DR. TAYLOR (Closing).—Both the discussers and I myself have appealed constantly to the past. This has been necessary because the concept which has been presented is not today a conventional one. Consequently, while this material was being worked up, the literature was gone over carefully to find as many supporters as possible for this thesis.

Actually, this subject is one which is very modern and one which in most branches of medicine is being actively investigated. I refer particularly to the vast group of disorders that are being studied under the general term of psychosomatic medicine. It has come to be believed that various types of disorder are due to the effects of emotion upon the smooth muscle of hollow viscera and blood vessel walls. In many of these other areas, methods of precision are gradually being developed and the factors affecting vascular and intestinal function are being measured. We are at a point where we may soon be able to apply similar concepts and methods to explain menstrual and other gynecologic symptomatology.

URETHRAL DIVERTICULUM IN THE FEMALE: A CLINICAL STUDY*

VIRGIL S. COUNSELLER, M.D., ROCHESTER, MINN.

(From the Division of Surgery, Mayo Clinic)

DIVERTICULA of the female urethra are not common, nor are they actually uncommon. The symptoms appear bizarre and yet they are diagnostic when carefully studied. It seemed to me, with these facts in mind, that the findings in 71 cases of diverticulum of the female urethra in which surgical treatment was employed at the Mayo Clinic and the impressions formed from study of these cases would be of interest to this association. A much larger group of patients who had small sacculations, deformities, and postoperative irregularities or scars which responded to local treatment and dilatations of the urethra were studied, but data on these patients are not included in this report.

This lesion has been known for many years but practically nothing on this subject appears in the current gynecologic literature. Most of the references to it and its management have been made by urologists and by some gynecologists who have written textbooks on gynecology which include some excellent discussions on urology of the female. Kelly[5] discussed this lesion in his textbook under the subject of suburethral abscess and also alluded to it as a "urethral urinary pocket" and urethral diverticulum. He described it as a pus pocket in the urethrovaginal septum from which pus was discharged by a slit in the posterior part of the urethra. Te Linde[7] and Wharton[8] presented excellent drawings of the lesion and its surgical management. Polak,[6] in his manual of gynecology, referred to it also as a suburethral abscess. Curtis[2] grouped diverticula and abscess pockets together and his statement regarding them is significant. He said, "Diverticula and abscess pockets connected with the urethra may have the same etiology. I have been gradually brought to this view through interest in the anatomy of the anterior vaginal wall. Let us not assume that abscess pockets are rare, for they are quite common indeed and most often they occur as sequelae of gonococcal infections." Furniss[3] has written, I believe, the most descriptive article on this subject and he included abstracts of the histories and findings in his ten cases. Herman and Greene,[4] in 1944, presented in detail the figures on incidence of the lesion and gave a good description of the symptoms and diagnosis. They reported six additional cases.

My studies of this lesion have caused me to believe that it is much more common than was previously believed and I have formed some impressions about its management which I wish to present briefly.

Most authors apparently have concluded that these diverticula are sequelae of repeated infections in a urethral gland and most likely are Neisserian in origin. After dissecting out a good number of these diverticula, I am of the opinion that they originate as congenital defects of the urethra and are subsequently influenced by trauma and nonspecific infections. They are analogous to diverticula of the intestinal tract or bladder in that they do not cause trouble unless they are unable to evacuate their contents completely. Any diverticulum that cannot empty itself will become infected and produce an abscess. Diverticula of the colon are excellent examples. A suburethral abscess to me is

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similar to diverticulitis of the colon with abscess formation. When the urethral orifice of the diverticulum is closed by an inflammatory process, then incision and drainage through the anterior vaginal wall may be sufficient for cure. Diverticula of the urethra never contain all the normal layers of the urethra. The sac has a mucosal lining; this, however, may be necrotic or ulcerative and difficult to identify. Further evidence that urethral diverticula are congenital in origin is found in the fact that some are of a large size, perhaps as long as the urethra and 1 cm. in diameter and yet there is no history that an abscess has been present in the region. From many of these urine can be expressed freely and it usually has an ammoniacal odor.

Another reason why I cannot agree with the usual theory concerning these diverticula is that I am skeptical regarding the presence of glands in the female urethra. I am inclined to agree with Cabot[1] that the urethra is devoid of glands except for Skene's glands located on each side of the external urethral meatus. I am equally certain that these Skene's glands have no connection whatever with these diverticula. I agree that infection has a definite role in the symptomatology and that the symptoms depend entirely on the degree of infection, which may be a low-grade infection or an acute abscess. But I doubt whether the infection has much to do with the development of the diverticulum. About 30 per cent of all women have some degree of urethritis, granular, cicatricial, or cystic. This incidence of infection can be easily, and I believe correctly, explained on the basis of the exposed position of the urethra.

Trauma to the urethra and infection, I believe, are most commonly the exciting etiologic factors in the production of symptoms referable to a urethral diverticulum. Trauma results from coitus and childbirth. In my series of 71 surgically treated cases, all except five of the patients were married and 80 per cent had had children. In only three cases had Neisserian infection been present, so that the inflammatory process in this group must be classed almost exclusively as nonspecific. For this reason, I believe that in the future the diverticulum with abscess should be regarded as a nonspecific lesion unless proved to be otherwise.

The average age of the 71 patients was 41 years. Thirty patients were from 31 to 40 years of age; 27 from 41 to 50 years of age; 6 were 30 years of age or less and 8 were more than 50 years of age. None of the patients were children.

Symptoms

The duration of symptoms is important. Symptoms may exist for only a few weeks, and can last for thirty-three years or more, as in one of my cases. Most of the patients in my group had symptoms for more than five years; the usual story was five to ten years. The cardinal symptoms were pain and frequency of urination, leakage of urine, dyspareunia and, finally, a vaginal mass.

The urinary symptoms may be mild to severe. Often the urethra does not show any local inflammation at all but the voided specimen will contain large amounts of pus even though contamination from the vagina is excluded. The catheterized urine may be entirely negative and this fact may lead to a mistaken diagnosis. On account of the symptoms of urethritis and without much evidence of anything else, the urethras of most of the 71 patients in my group had been excessively treated with local applications, heat, and tampons.

Pain is a significant symptom and its presence should make the physician at least suspect the presence of a diverticulum of the urethra. It is of 4 types: (1) low abdominal or suprapubic, like that usually produced by cystitis; (2) perineal, which appears to extend down through the perineal region and rectum; (3) vaginal, which usually consists of a sense of pressure or weight in the vagina; and (4) pain which frequently darts upward from the urethra and through the vagina to the pelvic organs. Pain in the sites and types described appeared in 55 per cent of the 71 cases.

Leakage of urine or a discharge from the urethra was noted in 40 per cent of the cases. Some patients considered this condition a stress incontinence. The characteristic leakage is that which immediately follows urination, when the patient thinks she has completely evacuated her bladder and is surprised to find a subsequent involuntary discharge of a small amount of urine.

Dyspareunia was experienced by 10 per cent of the patients and was a complaint of those who had rather acute inflammatory reactions in the anterior vaginal wall.

A mass in the anterior vaginal wall was noted by 40 per cent of the patients. These masses were not all abscesses and surprisingly enough were not always especially tender. The mass may be urine, pus, and sometimes multiple calculi. If the history indicates that a diverticulum has been present for a number of years, there often will be a sense of pressure in the vagina and the anterior vaginal wall may be indurated. This induration may simulate a mass but a true mass may not be present.

The severity of the complaint is also significant. It is out of all proportion to that which the physical findings concerning the urethra indicate should actually be produced. There is no relation between the complaint and menstruation.

Diagnosis

Vaginal examination with careful palpation of the anterior vaginal wall under the entire urethral region may reveal some induration or a definite mass. Pressure on the mass will cause foul-smelling urine or pus to exude from the external urethral orifice unless the orifice of the diverticulum has been occluded by the inflammatory process. If there is only induration, the diverticulum can be more easily identified if a urethroscope is placed in the urethra and then the urethra is palpated over it.

Cystoscopy is not always successful in identifying the diverticulum. The orifice sometimes is not easily seen. In one case, cystoscopy was performed seven times before the orifice of the diverticulum could be seen and several have had cystoscopic examinations more than one time. There may be more than one opening to the diverticulum. The opening is usually in the middle third of the urethra and in the midline. However, in some of the 71 cases the opening was on one or another side of the midline. The diverticulum may extend in any direction along the urethra and occasionally almost encircle it. In a few cases, the orifice of the diverticulum was in the posterior portion of the urethra and the diverticula were situated under the trigone of the bladder. When the orifice can be identified, a small lead catheter should be coiled in the diverticulum and a roentgenogram taken of it. Also, injection of an opaque medium into the diverticulum, if possible, followed immediately by a roentgenogram aids considerably in determining the size and direction of the diverticulum.

Treatment

It has been our experience at the clinic that any local treatment, such as massage, dilatation, or instillations, is of no value when a real diverticulum exists. Transurethral incision of very small diverticula for more adequate drainage may be useful. The best treatment, however, is complete surgical

excision of the diverticulum and repair of the urethra. This can be accomplished in practically all cases except the few in which abscesses are present. In these few instances, the orifice of the diverticulum may be necrotic and cannot be closed by suturing. A urethral fistula then would result and this fistula should be repaired only after all evidence of inflammation has subsided. When the inner wall of the diverticulum extends posteriorly along the urethra, it usually is intimately attached to the urethra and no attempt should be made to separate the wall of the diverticulum from the urethra. To do so may cause multiple fistulas.

Surgical excision may be difficult unless the diverticulum can be seen readily. A retention catheter, No. 18 to 22, should be placed in the bladder as a preliminary procedure, so that the identity of the lumen of the urethra is always known. The anterior vaginal wall should be mobilized, preferably between two small clamps or hemostats and the anterior vaginal wall should be opened from just behind the external urethral meatus to the area of the trigone of the bladder. The fascia over the urethra is incised and separated from it and the vaginal wall, as in repair of urethrocele. As the surgeon cuts with a sharp scalpel directly down on the urethra, the diverticulum as a rule begins to bulge into view. With the catheter in place in the urethra, the diverticulum can be distinguished from the urethra. At this point the diverticulum can be grasped with a clamp and further separated from the surrounding tissues.

When the diverticulum is definitely identified, it should be opened and its contents, if any, evacuated. The extent and direction of the sac can be accurately determined by examination of the interior of the sac under direct vision. The relation of the inner wall to the urethra can be observed. If the diverticulum is firmly adherent to the urethra and at all inflammatory, all of the sac should be excised except that small segment along the urethra. The orifice in the urethra can be closed with interrupted fine catgut sutures. This region should be reinforced by a running suture which closes the fascia over the entire urethra including the defect. A catheter is maintained in the urethra for only four to five days; the patient then is advised to go to the bathroom and void. Subsequent catheterizations are inadvisable.

Urethrovaginal fistulas which occur subsequent to repair of cystocele, urethrocele, or vaginal hysterectomy could easily be due to a urethral diverticulum which was overlooked previously. I cannot tell from my studies on fistulas which ones may have been caused in this manner but I strongly suspect that the number is greater than physicians may have thought previously.

Comment

Diverticula of the female urethra in all probability originate from congenital defects in the urethra just as do diverticula in any other part of the body. They may be quiescent, but if nonspecific infection and trauma disturb them in any way, symptoms develop. The exposed position of the female urethra and the high incidence of nonspecific urethritis make it likely that, if a diverticulum is present, it will sooner or later produce symptoms and require surgical excision for a cure. These conclusions are formulated on the basis of 71 patients who have been treated surgically.

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Discussion

DR. LOUIS E. PHANEUF, Boston, Mass.—Dr. Counseller's report is based on 71 cases of diverticulum of the female urethra in which surgical treatment was employed at the Mayo Clinic. Contrary to the opinion of most authors on the subject who imply that diverticula are the result of repeated infections in a urethral gland, due largely to Neisserian invasion, Dr. Counseller believes that they originate as congenital defects of the urethra, which are subsequently affected by trauma and nonspecific infections. He further compares a suburethral abscess to diverticulitis of the colon with abscess formation. He strengthens his point against the acceptance that a diverticulum develops as the result of infection of a urethral gland by the statement that the female urethra is devoid of glands, other than Skene's glands, one of which is found on each side of the urinary meatus. I am in agreement with him in the above contentions, and also in the fact that Skene's glands have no relation to these diverticula. Trauma from coitus and childbirth and infection are held to be the common exciting etiologic factors referable to urethral diverticula.

As to the symptomatology, the essayist lists pain, urinary frequency, leakage of urine, dyspareunia, and vaginal mass. The opening of the diverticulum in the urethra is stated to be in the middle third of the urethra, in the middle line.

Dr. Counseller states that diverticula of the female urethra are not common, nor are they actually uncommon. On the basis of my own experience, I have always considered this disorder to be quite uncommon. A review of the records at the Carney Hospital, from June, 1937, to September, 1947, showed only four cases during approximately ten years.

CASE 1.—A woman, 35 years of age, mother of three children, who had an infected diverticulum of the urethra and a cystocele. The diverticulum was resected, the urethral opening closed, the cystocele repaired, and constant bladder drainage instituted. There was satisfactory healing and the patient was discharged cured.

CASE 2.—A married, nulliparous woman, 35 years of age, had an infected diverticulum of the urethra and uterine fibromyomas. Operation was performed on May 13, 1938, and consisted of resection of the diverticulum and reconstruction of the urethra over a catheter, this being unsuccessful. There followed four operations in an attempt to close the resulting fistula. All failed because of the great loss of urethral tissue at the first operation. Supravaginal hysterectomy and bilateral salpingo-oophorectomy were subsequently performed for fibromyomas of the uterus, pelvic inflammatory disease, and endometriosis. On Sept. 16, 1943, the left ureter was transplanted in the sigmoid. On Sept. 9, 1944, the right ureter was transplanted in the sigmoid. In July, 1947, intravenous pyelograms showed the kidneys in satisfactory condition. The patient had urinary control and the nonprotein nitrogen was 28 to 40 mg. per cent. Examination made in April, 1948, showed the physical condition to be satisfactory.

CASE 3.—This was the case of a married, nulliparous woman, 58 years of age, with an infected urethral diverticulum. The sac was dissected, opened, and the contents evacuated. The sac was resected, the urethral opening closed and the anterior vaginal wall sutured. Constant drainage was established. The healing was satisfactory and the patient was discharged cured.

CASE 4.—A married woman, 31 years of age, mother of three children, all delivered by cesarean section, had a diverticulum of the urethra. Operation consisted of excision of the diverticulum, conserving a strip 1 cm. in width from the sac. The opening in the urethra was closed in three layers, using the strip dissected from the diverticulum as a third layer in closing the defect. The anterior vaginal wall was sutured and suprapubic bladder drainage instituted. Satisfactory healing took place, and the patient was discharged cured.

Dr. Counseller's large series of 71 cases, in which surgical treatment was employed, probably the largest series reported, allows him to speak with authority on the subject.

DR. LAWRENCE R. WHARTON, Baltimore, Md.—Dr. Counseller's paper falls into two parts—the first dealing with the anatomic findings and his conclusions about etiology; and the second, with the clinical discussion.

Dr. Counseller's anatomic findings are interesting. Probably many women have small periurethral diverticula or crypts which are the foci that perpetuate chronic infections of the urethra and bladder. Some of these diverticula become large. The small ones are extremely hard to find, the large ones can be discovered easily by palpating the periurethral regions and by expressing the large quantity of pus, much more than would be contained in the urethra itself.

Whether these are all congenital diverticula or whether some begin as infected periurethral glands, is perhaps an academic question as far as therapy is concerned. Dr. Counseller does not believe there are normally any glands around the urethra, and hence leans toward the opinion that these diverticula do not originate in such normal structures.

The female urethra is a remarkable structure. It looks so simple. It is short, straight, and has a large caliber. And yet careful observers have reached contradictory opinions about its normal anatomy, especially about the presence of glands in its walls, with openings into the urethral lumen. I myself doubted the existence of periurethral glands (excluding Skene's), until I read the article by Dr. Huffman presented before this Society one year ago. It is difficult to doubt the existence of periurethral glands after studying Dr. Huffman's work.

If there are normally such glands around the urethra, then there is no reason why such glands should not behave as glands do anywhere else, become infected, distended by the occlusion of their ducts, and transformed into cysts. In other words, one does not have to assume that all diverticula are congenital, if one accepts the proposition that there are usually small glands in the urethral wall.

Consequently, I would be inclined to modify Dr. Counseller's view, and state that these diverticula may be either congenital or acquired, and that the small multiple crypts and diverticula probably originate in periurethral glands.

I do not believe it is possible to distinguish congenital from acquired diverteiula by clinical means, with absolute certainty. This would apply especially to such conditions when they occur in adults, and all of Dr. Counseller's cases were in adults. Fortunately, a few such cases have been found in infants and children. Dr. Thos. S. Cullen published a paper on "Urethral Diverticulum" in 1894. Dr. Cullen had abstracted the literature and found several cases in children—one in an infant 1 year old. Such observations naturally lend weight to Dr. Counseller's view that they are congenital, although it does not exclude the possibility that some may be acquired.

The discussion concerning their origin may be possibly academic but there is nothing academic about the clinical problem they present. The persistence of these infected diverticula and the diagnostic difficulty are shown by our experience. I am certain that in a considerable number of women, chronic recurring cystitis is due to these insidious urethra lesions. I am equally certain that I have missed the diagnosis in a good number. Some of these women have wandered from clinic to clinic, trying to find the cause of their cystitis, without success, for we have all missed these small urethral lesions. Dr. Counseller says that his patients have had symptoms for five to ten years, on the average, and that he has cystoscoped some of them nine times before finding the diverticulum. This is a general experience.

DR. N. SPROAT HEANEY, Beverly Hills, Calif.—There is one symptom that I think is pathognomonic, and that is the feeling that the patient has for a short time after voiding. While urinating, she fills up the diverticulum and then the diverticulum will slowly empty and the patient gets wet.

A point also to observe is that, if the patient voids before examination and you strip the urethra, as you ordinarily do to see whether there is pus in the urethra, you will milk out a half teaspoon or so of urine flecked with pus. That, I think, is the most important finding leading you to suspect that there is a diverticulum of the urethra.

Original Communications

THE SURGICAL ANATOMY OF EXTRAPERITONEAL CESAREAN SECTION

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THE aim of extraperitoneal cesarean section is adequate exposure of the lower uterine segment for delivery of the child without accidental injury to the peritoneum, bladder, or ureters. Because the technical difficulty of the procedure is governed largely by the anatomic variations encountered, knowledge of the regional anatomy and its vagaries is important.

The material presented in this essay results from experience with forty-nine extraperitoneal operations of all major types: the Latzko,[1] and Latzko as modified by J. C. Irwin[2] and J. F. Norton,[3] the Waters[4] and the technique described. Five operations were performed in the absence of labor, one at six and one-half months' gestation, and the others approximately at term. Three were secondary cesareans following one primary extraperitoneal and two primary transperitoneal procedures. The peritoneal staining technique devised by one of us[5] facilitated the study of anatomic variations in twenty-one operations, and in all the above methods except the Latzko.

For complete exposition, the material is presented from four interlocking points of view: anatomic description, planes of dissection, anatomic approaches to the lower uterine segment, and the technique developed from consideration of the foregoing.

Anatomic Description

Modern extraperitoneal cesareans are ideally accomplished by separating the intact peritoneum with portions of its enveloping fascia from the anterior abdominal wall, bladder, and lower uterine segment. The resulting structure is termed the *peritoneofascial flap,* and during its dissection two components, the anterior (parietovesical) and posterior (uterovesical) transverse peritoneofascial folds may usually be recognized. Fig. 1 depicts the approximate area of peritoneum and fascia detached in forming the peritoneofascial flap.

1. *The Peritoneum.*—The peritoneum is composed of an inner layer of simple squamous epithelium or serosa, and an outer subserous layer of fibroareolar connective tissue.[6, 7, 8] The serosa descends from the dome or supravesical area of the partially distended bladder to form (Fig. 1) a parietovesical peritoneal reflection anteriorly, right and left paravesical reflections laterally, and a uterovesical peritoneal reflection posteriorly.

The configuration and level of attachment of the peritoneal reflections or fossas varies considerably. When exposed by dissection, the parietovesical reflection usually lies symmetrically over the bladder. Most often it presents a downward convexity (Fig. 2a, c) but occasionally the convexity faces upward (Fig. 2b). If the paravesical reflections differ in their level of attachment, the parietovesical reflection is correspondingly asymmetrical (Fig. 2d). The uterovesical reflection ordinarily extends lower on the bladder than the parietovesical reflection (Fig. 2a, b); but the reverse relationship may exist (Fig. 2c). In our experience, the uterovesical reflection always lies in a fairly even transverse manner over the lower uterine segment. The general level of peritoneal attachment may lie much higher or much lower on the bladder than shown in Fig. 2.

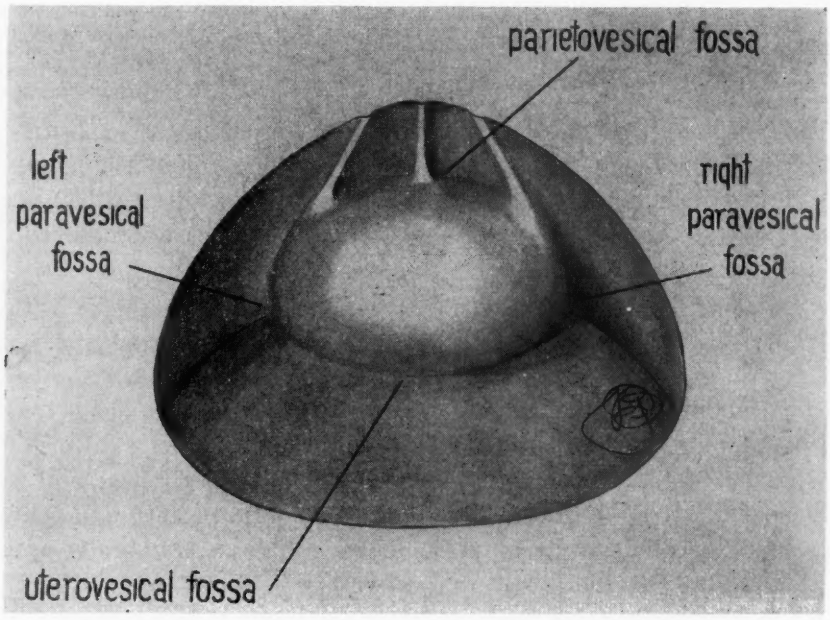

Fig. 1.—The peritoneal aspect of the structures encountered in extraperitoneal cesarean section (abdominal wall, bladder, urachus, lateral umbilical ligaments and lower uterine segment). The partially distended bladder brings out the peritoneal fossas. This figure approximates the area of peritoneum and fascia separated in forming the peritoneofascial flap.

The outer connective tissue layer of peritoneum exhibits a fibroareolar nature varying in thickness and density according to location and the individual (Fig. 3); it contains varying amounts of adipose tissue.

Anteriorly subserous or fibroareolar peritoneum is applied to the transversalis fascia covering the recti muscles. It is more areolar than fibrous in character and may contain properitoneal fat. In the midline of this layer, the terete fibrous urachus, a remnant of the embryonic allantois, extends from the vertex of the bladder to the umbilicus.

Over the bladder dome, or supravesical area, areolar tissue may predominate (Fig. 3a, a′)—a condition greatly simplifying extraperitoneal cesarean; but it is usually absent to some extent (Fig. 3b, b′, c, c′), with the result that, for clinical purposes, a varying area of serous peritoneum is inseparable from perivesical fascia. In direct proportion to its degree and extent, adherence of these structures increases the formidability of operation.

Loose areolar tissue separates the serosa of the uterovesical fossa above from the junction of the perivesical and periuterine fascias below; this is the site of initial incision for the bladder flap when performing low cervical transperitoneal cesarean section. When the anterior border of this area exhibits adherence of serous peritoneum to perivesical fascia, a definite posterior transverse peritoneofascial fold is formed. Along the posterior border of this area, serous peritoneum is attached to periuterine fascia with the intervention of minimal areolar and no adipose tissue; in our experience, this is the only constant area of adherence.

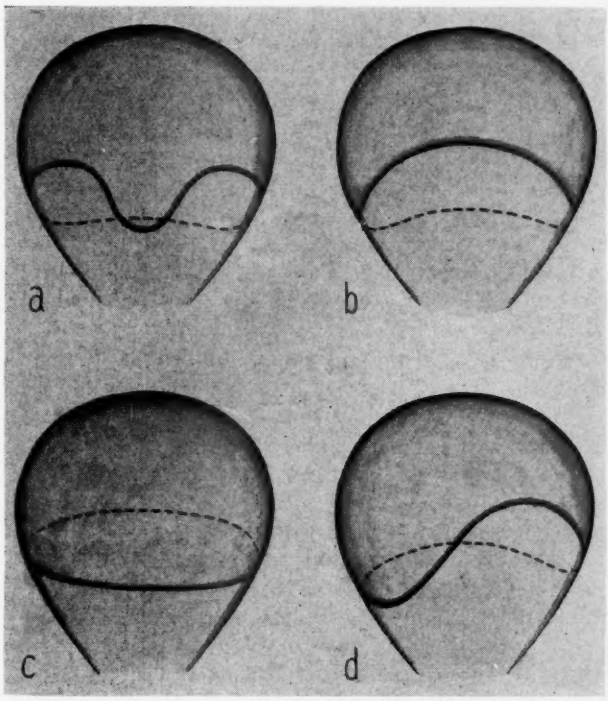

Fig. 2.—Variations in configuration of the peritoneal bladder reflections. *a* and *c:* Common downward convexity of the anterior or parietovesical reflection. *b:* Uncommon upwardly convex parietovesical reflection. *d:* Rare asymmetrical parietovesical reflection. The posterior or uterovesical reflection lies symmetrically in a transverse manner over the lower uterine segment; it usually extends lower on the bladder than the parietovesical reflection (*b*) but the reverse relationship may exist (*c*).

2. *The Fascias.**—The transversalis fascia lining the musculature of the lower abdominal wall extends into the pelvis as endopelvic fascia. This provides fascial covering for the parietal pelvic walls and forms membranous envelopes about the bladder, ureters, and uterus: the perivesical, periureteral and periuterine fascias, respectively.

The transversalis and anterior perivesical fascias blend intimately inferior to the parietovesical peritoneal fossa, to take part in formation of the anterior (parietovesical) transverse peritoneofascial fold. The round, fibrous, lateral umbilical ligaments (obliterated hypogastric arteries), running from the anterolateral aspects of the bladder to the umbilicus, mark the lateral boundaries of this fold. In the midline, a short but variable distance posterior to the parieto-

*As employed in this essay, the term "fascia" denotes visible and palpable sheets of connective tissue as they are encountered at the operating table.

vesical fascial fold, the urachus, which may be patent, arises from the perivesical fascia and proceeds in the areolar subserous peritoneum, just anterior to the serous peritoneum, to the umbilicus.

The perivesical fascia is intimately coapted to bladder muscularis throughout and in the supravesical area, where it may be exceedingly thin, it is often just as closely coapted to varying areas of serous peritoneum (Fig. 3b, b′, c, c′). It has been observed in most operations performed with the peritoneal staining technique that in such areas the perivesical fascia may be so thin that bladder and serous peritoneum can be separated only by dissection in the outer layers of vesical muscularis. This fact is not, however, a valid reason for performing the major portion of the dissection in that plane.

Posteriorly, the perivesical and periuterine fascias blend loosely inferior to the uterovesical peritoneal fold to take part in forming the posterior (uterovesical) transverse peritoneofascial fold. Here the serous peritoneum is attached by loose areolar tissue to the plane of junction of these fascias and adherent posteriorly to periuterine fascia, while it may or may not be adherent anteriorly to the perivesical fascia.

Lateral to the bladder on either side and inferior to the paravesical fossa lies the paravesical space. During the last trimester of gestation it roughly approximates an inverted three-sided pyramid bounded superiorly by the peritoneum of the paravesical fossa, medially by the membranous perivesical and posteriorly by the membranous periuterine fascias, and anterolaterally by the fascias of the abdominal and pelvic walls. It contains abundant fibroareolar tissue derived from the fascial structures forming its boundaries, and along the junction of the perivesical and periuterine fascias lies a constant mass of adipose tissue—the so-called yellow chicken fat. An inferior extension of the paravesical space contains the ureter as it emerges from the bladder to course laterally, posteriorly and superiorly along the pelvic wall. A posterolateral extension of the paravesical space contains the iliac and uterine vessels, and again the ureter. As performed in modern extraperitoneal operations, dissection of the paravesical space rarely exposes either blood vessels or ureter; however they can be demonstrated after the uterus has been emptied.

Planes of Dissection

In describing their technique, early operators implied use of a plane of dissection between the peritoneum and bladder. As might be expected from their limited knowledge of the regional anatomy, these surgeons regarded extraperitoneal cesarean as a theoretically ideal but impracticable operation.

In 1940, Waters popularized a satisfactory cleavage plane between perivesical fascia and bladder muscularis. Its particular disadvantage lies in disruption of bladder vessels with annoying though not serious bleeding, in exposure of bladder mucosa and occasional violation of the bladder cavity. Furthermore this cleavage plane does not eliminate accidental opening of the peritoneum.

In 1942, Ricci and Marr[9] advocated dissection within the layers of the perivesical fascia. This plane of cleavage would be ideal if it could be consistently pursued; but the intimate union of serous peritoneum, a thin perivesical fascia and vesical muscularis often encountered in the supravesical area prevents consistent use of this plane of dissection alone.

There are anatomic limitations to any single plane of dissection. In the first place, dissection of the paravesical space, which must be cleared to provide the exposure requisite to any modern extraperitoneal cesarean technique whether initiated by way of the anterior (paravesical) or medial (supravesical) approach to that space, is neither within the layers of the perivesical fascia nor between

bladder fascia and muscularis. In the second place, variations in the character of subserous peritoneum and perivesical fascia may result in such close apposition of serous peritoneum and bladder muscularis that dissection within the layers of the perivesical fascia is impossible. In the third place, proponents of

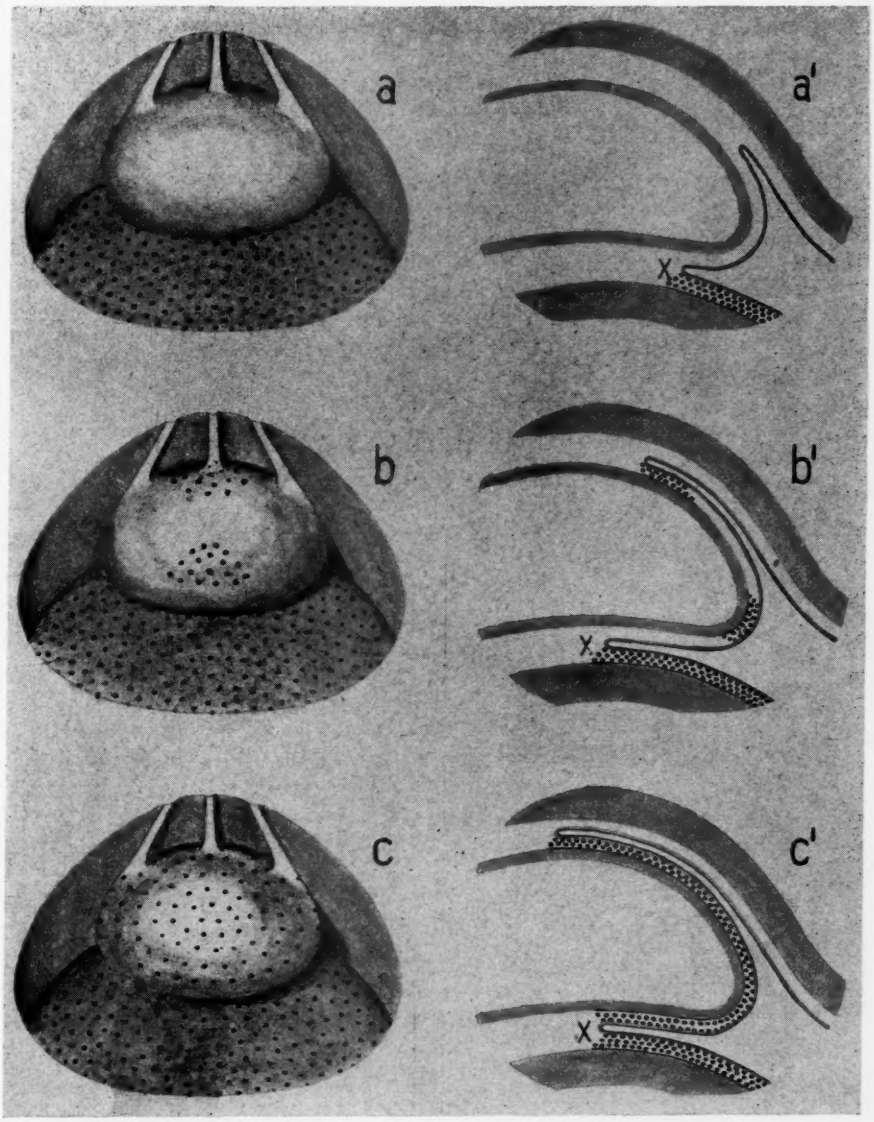

Fig. 3.—Variations in adherence of serous peritoneum to vesical fascia and muscularis. Stippling indicates adherent areas. *a* and *a'*: Abundant areolar tissue in subserous peritoneum and complete lack of adherence between serous peritoneum and vesical fascia. *b* and *b'*: Moderate areolar tissue in subserous peritoneum and small area of adherence between serous peritoneum and vesical fascia. *c* and *c'*: Minimal areolar tissue in subserous peritoneum and extensive area of adherence between serous peritoneum and vesical fascia. Note the constant area of adherence between peritoneum and uterine fascia. "x" is the constant area of areolar tissue just inferior to the uterovesical peritoneum.

these cleavage planes (within the perivesical fascia, or deeper) refer to the hernialike peritoneal sac followed during dissection. It is obvious that dissection revealing the peritoneum as a hernialike sac is carried out, for the most part, within the fibroareolar component of the peritoneum and not within the fascial or muscular coverings of the bladder.

In fact, it is fairly certain that most extraperitoneal cesareans are performed successfully only by the planned or chance use of several planes of dissection.

Anatomic Approaches to the Lower Uterine Segment

Most modern extraperitoneal cesarean techniques provide bilateral exposure of the lower uterine segment adequate for a low transverse cervical or low vertical incision. There are only two possible initial paths of approach: by the paravesical space (the paravesical approach) or by the anterior transverse fold

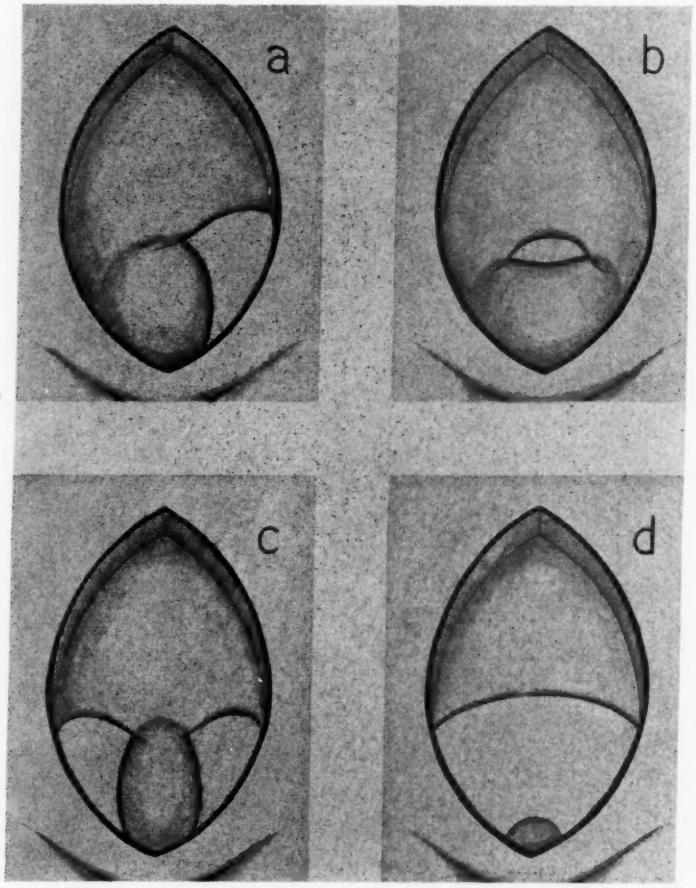

Fig. 4.—Diagrammatic representation of the unilateral paravesical (a), the supravesical (b), and the bilateral paravesical (c) approaches to the lower uterine segment. *d:* Adequate exposure of the lower uterine segment which may be obtained using any of these approaches—the unilateral paravesical by subsequent dissection of the supravesical and opposite paravesical areas; the supravesical by subsequent dissection of both paravesical areas; the bilateral paravesical approach by subsequent dissection of the supravesical area.

and the supravesical area (the supravesical approach). Ultimately, in complete dissections, the supravesical area and both paravesical spaces are dissected out, the bladder lies almost entirely free except for its basal attachments, and final exposure of the lower uterine segment is the same.

The paravesical approach exemplified by the Latzko technique (Fig. 4a) provided inadequate unilateral exposure which jeopardized the peritoneum, bladder, and ureter. An incomplete operation at best, it offered for several

decades the only practicable route to the lower uterine segment. During this period, extraperitoneal cesarean section was infrequently attempted and then only as a last resort.

The paravesical operation described by Irwin completes the Latzko procedure by dissecting over the dome of the bladder and clearing the opposite paravesical space. Satisfactory exposure of the lower uterine segment results.

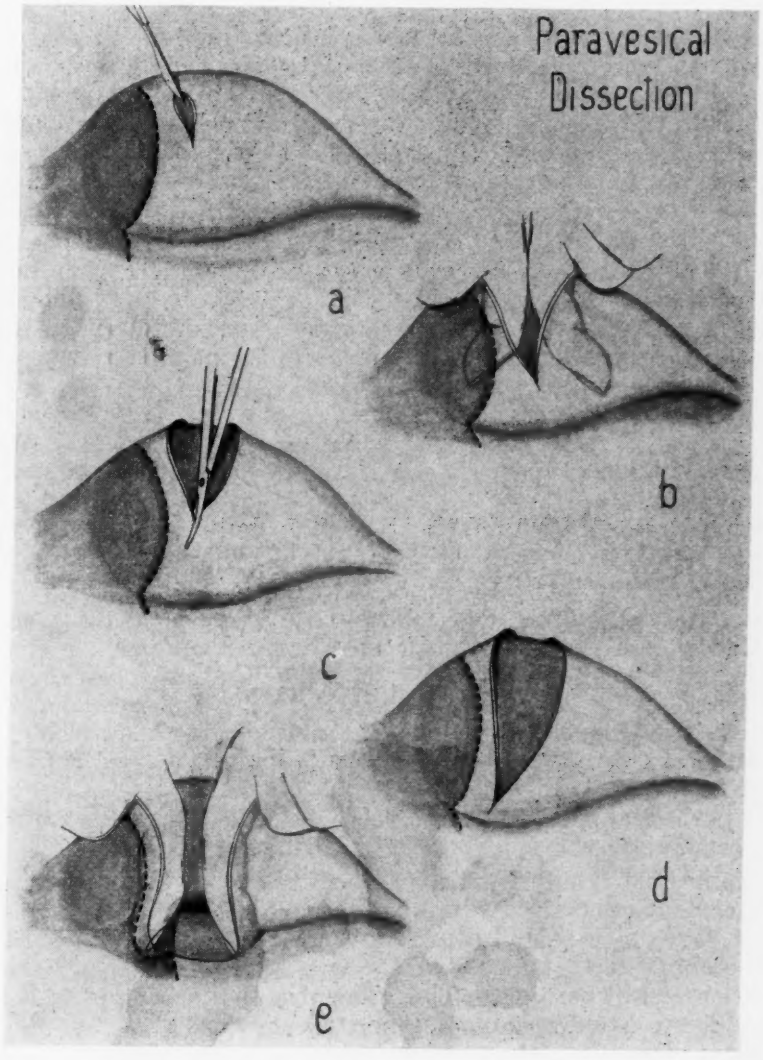

Fig. 5.—The paravesical dissection. The distended bladder and its overlying transversalis fascia have been separated by blunt dissection from the anterior abdominal and lateral pelvic walls to the chicken fat area in the paravesical space on both sides. *a:* Incision of the transversalis and outer layers of perivesical fascia below the anterior peritoneofascial fold. *b, c, d,* and *e:* Extension of this plane of cleavage within the perivesical fascia to the medial aspect of the paravesical space. This dissection is then repeated on the opposite side.

The supravesical approach (Fig. 4b) advocated by Waters exhibits initial dissection of the supravesical area with subsequent clearing of both paravesical spaces. Its technical disadvantage lies in the primary attack on the supravesical area which usually presents the most difficult dissection.

In our experience, a bilateral paravesical dissection (Fig. 4c) followed by retrovesical separation of the bladder from the lower uterine segment, with dis-

section of the peritoneum from the bladder in the supravesical area and finally from the lower uterine segment, has proved the most reliable procedure. It takes advantage of the more constant anatomic relationships in attacking the paravesical and retrovesical dissections first; it defers dissection in the usually adherent supravesical area until the best possible control over the structures involved has been obtained.

Operative Technique

1. *Preparation of the Patient.*—With the patient anesthetized and in lithotomy position, the vulva and vagina are prepared with antiseptics, the obstetric condition of the cervix and the presenting part are determined. A Malecot catheter attached to a suitable apparatus for distending and emptying the bladder is introduced into that organ and tested. The abdomen is prepared, the patient is placed in moderate Trendelenburg position and sterile drapes arranged.

2. *Incision of the Anterior Abdominal Wall.*—The bladder having been filled with 150 to 250 c.c. of sterile water or saline solution, a midline incision is made from the symphysis pubis to the upper pole of the distended bladder. The incision is carried to the rectus sheath, hemostasis is attended to and skin towels are clipped in place. The rectus sheath is incised in the midline and both recti muscles dissected out.

A midline incision offers the following advantages: 1. it avoids the deep epigastric vessels; 2. it permits equal access to both sides of the pelvis; 3. it permits approximation of the recti muscles when closing the abdomen, a matter of some importance to gravidas with potential or actual diastasis recti; 4. it is complementary to the midline incision of prior or subsequent gynecologic surgery; and 5. with the exception of the Pfannenstiel incision, which we occasionally use, it produces the most elegant cosmetic result.

3. *The Paravesical Dissections.*—By blunt dissection, the transversalis fascia covering the distended bladder is separated laterally on one side from the posterior surfaces of the recti muscles to the yellow chicken fat in the paravesical space just lateral to the junction of the periuterine and perivesical fascias. During this dissection, the transversalis fascia diffuses into the areolar connective tissue of the paravesical space. The same procedure is carried out on the opposite side of the distended bladder.

If the peritoneal staining technique is used, the bladder is emptied at this point, the peritoneofascial flap is stained, and the bladder refilled.

At a point below the parietovesical peritoneal reflection, a short transverse incision is made through transversalis fascia and the outer layers of perivesical fascia (Fig. 5a); this incision is discontinued as the vesical veins come into view.

If the staining technique is used, the incision is made about 2 cm. below the stained parietovesical peritoneal fold; otherwise, the incision must be well down on the bladder to avoid opening the peritoneum.

By blunt dissection, the cleavage plane within the perivesical fascia is developed laterally to the point of junction of the periuterine and perivesical fascias (Fig. 5). This point will be medial to the yellow chicken fat previously identified. The layer of fascias (transversalis and outer perivesical fascias) thus isolated will contain a low-lying paravesical peritoneal reflection; the fascia is divided below the reflection (Fig. 5c and 5d). The paravesical peritoneum is wiped upward as far as possible (Fig. 5e). This completes the paravesical dissection on one side; it is repeated on the other side and the bladder emptied.

4. *The Retrovesical Dissection.*—The bladder is maintained in its collapsed state for the remainder of the operation (Fig. 6a). With the palpable collapsed bladder retracted medially by a finger and the parietes retracted laterally with a Richardson retractor, the fibroareolar connective tissue overlying the lower

uterine segment is frayed with Metzenbaum scissors at a point below the uterovesical peritoneal reflection until the glistening purplish-tinged layers of the periuterine fascia are exposed (Fig. 6b). This procedure is repeated on the opposite side of the bladder.

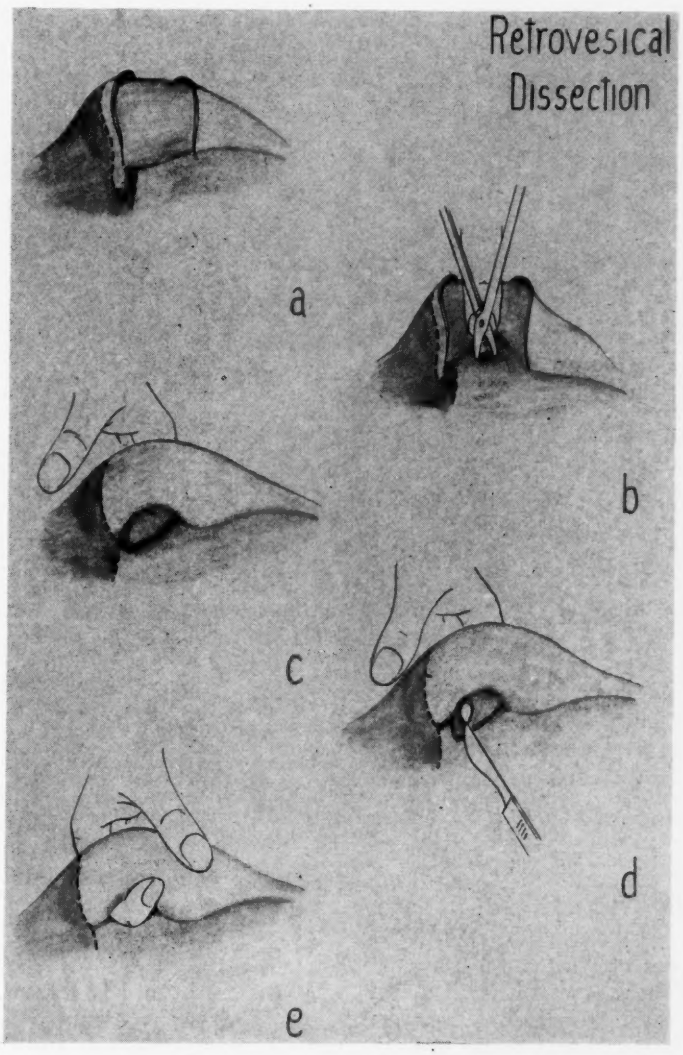

Fig. 6.—The retrovesical dissection. *a:* The collapsed bladder. *b:* With the bladder retracted medially by a finger, the fascias over the lower uterine segment are frayed until the glistening purplish-tinged uterine fascia is exposed. This step is repeated on the opposite side. *c:* The index finger inserted retrovesically between uterine and vesical fascias (in the areolar connective tissue region inferior to the uterovesical peritoneum) from one paravesical space to the other. *d:* Incision of residual fascia over the tip of the retrovesical finger, thus connecting the two paravesical spaces retrovesically. *e:* The collapsed bladder raised from the lower uterine segment.

A finger can then be introduced between the easily separated layers of perivesical and periuterine fascia from one side to the other (Fig. 6c) and the two paravesical spaces made continuous retrovesically by sharp dissection of the remaining tissues over the finger tip (Fig. 6d). The bladder can now be raised from the lower uterine segment (Fig. 6e); it is attached to peritoneum only at its supravesical area.

5. *The Supravesical Dissection.*—Since anatomic variations in the supravesical area are marked, its dissection can be surprisingly easy or discouragingly difficult. When abundant areolar and little fibrous tissue connect serous peritoneum and bladder fascia, separation of these structures is readily accomplished by transverse division of the entire intervening fibroareolar tissue mass (Fig. 7a).

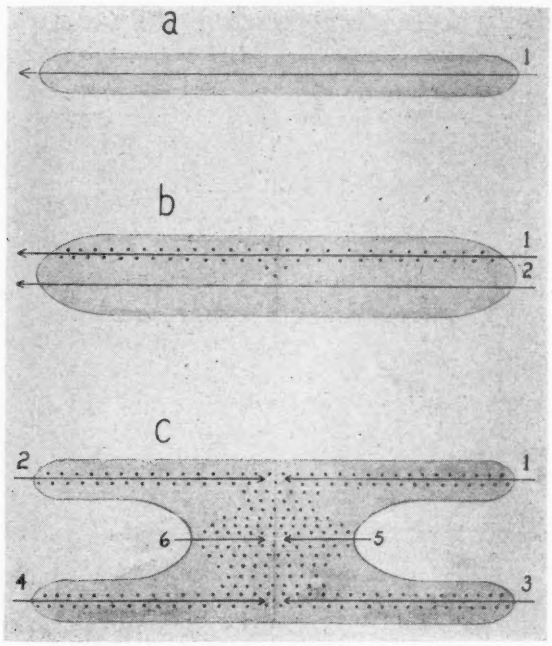

Fig. 7.—The supravesical dissection: plans of attack. Diagram of more common plans of attack on the supravesical area. Stippling indicates areas of adherence. *a:* The case with abundant areolar subserous peritoneum and no adherence of serous peritoneum to vesical fascia. *b:* The case with adherence of serous peritoneum to perivesical fascia along the anterior transverse peritoneofascial fold. *c:* The common and usually difficult case with no areolar subserous peritoneum and extensive adherence of serous peritoneum to vesical fascia in the supravesical area and along both anterior and posterior transverse peritoneofascial folds.

When serous peritoneum and perivesical fascia or bladder muscularis are intimately coapted by virtue of almost complete absence of subserous fibroareolar peritoneum and exceptional thinness of the perivesical fascia, an orderly plan of dissection is of value. Most individuals present areas of adherence along the anterior transverse fold and in the supravesical area. If adherence is slight, it may be possible to divide these structures and then the posterior transverse fold in turn from side to side (Fig. 7b). When adherence is marked, however, it is safest to dissect each structure individually from its lateral aspect toward the midline where the most intimate coaptation may be expected (Fig. 7c). Thus, dissection of the central supravesical area which includes the urachus is usually the last step in separation of the peritoneum from the bladder.

There are several maneuvers which are helpful in performing the supravesical dissection. When the retrovesical dissection has been accomplished, traction with the finger tips introduced in a medial direction behind the anterior transverse fold brings that structure into relief and facilitates its dissection (Fig. 8a). Occasionally the anterior transverse fold can be easily divided from one side to the other by sharp dissection (Fig. 8b). Rotation of the bladder and attached peritoneum through approximately 180° with sharp dissection of

the posterior transverse fold from the bladder is a useful maneuver in difficult dissections (Fig. 8c). At times, a finger can be gently forced between bladder and peritoneum so as to expose and facilitate division of the connecting fascia (Fig. 8d). At any point, dissection may usually be accelerated by traction on

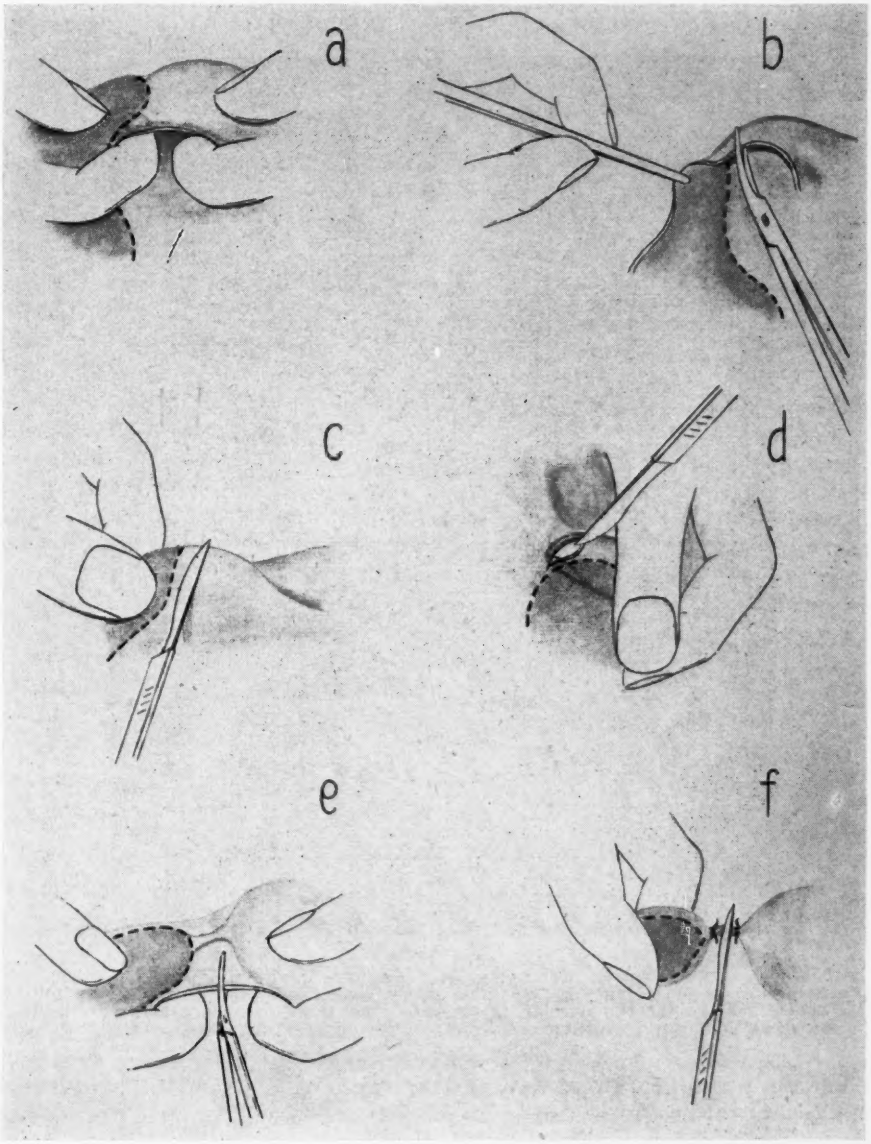

Fig. 8.—The supravesical dissection: methods. Maneuvers useful for the supravesical dissection. *a:* Exposure of the anterior transverse peritoneofascial fold by traction on the bladder and the peritoneofascial flap. *b:* Sharp dissection of the anterior transverse fold from the bladder. *c:* Rotation of the bladder to bring its posterior surface into view; sharp dissection of the posterior transverse peritoneofascial fold from the bladder. *d:* Sharp dissection over finger tip of the fibroareolar tissue between bladder and peritoneum. *e:* Dissection of fascia in supravesical area approaching the urachus. *f:* Division of the urachus between ligatures.

the bladder and the peritoneofascial flap which accentuates the joining fascia (Fig. 8e). Final separation of the bladder from the peritoneofascial flap is frequently accomplished by division of the urachus; if the urachus is more than

a fibrous cord, it is divided between ligatures of fine chromic gut (Fig. 8f). In some cases it may be necessary to separate the visible serous peritoneum from an exceedingly thin adherent perivesical fascia and bladder muscularis by dissecting in the outer layers of vesical muscularis; in easier dissections this is necessary in only a small area about the urachus, but in more difficult ones such dissection may be required over an extensive area.

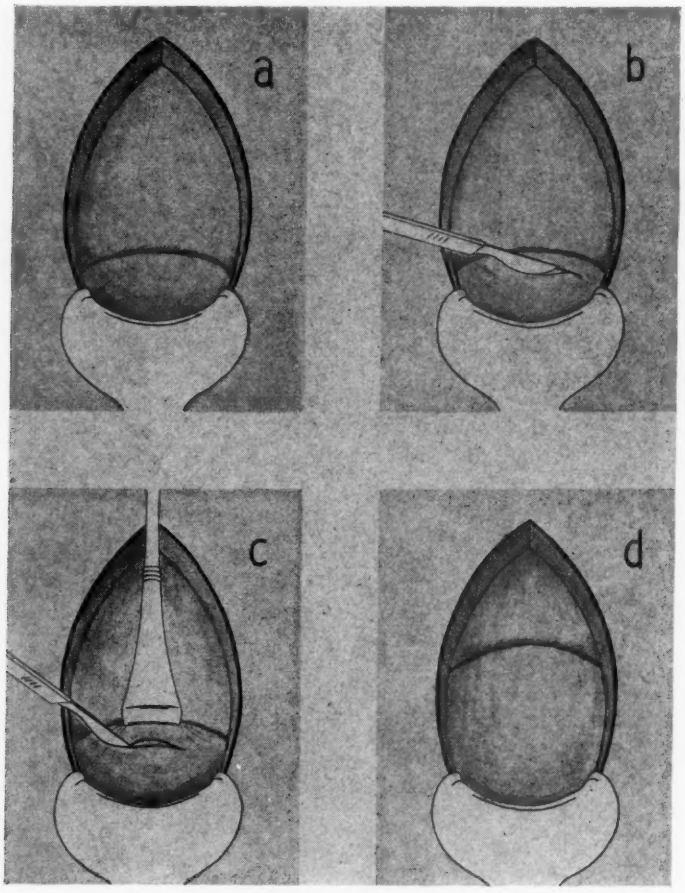

Fig. 9.—Exposing the lower uterine segment. *a:* The bladder has been placed under the symphysis behind a Doyen retractor. *b:* Incising the uterine fascia below the peritoneofascial flap. *c:* Further incision of the uterine fascia, allowing the peritoneofascial flap to be raised with a Richardson retractor. *d:* Final exposure of the lower uterine segment.

When the peritoneofascial flap has been separated from the bladder, it lies adherent to the lower uterine segment in a transverse manner (Fig. 9a). The periuterine fascia inferior to the fold is incised transversely (Fig. 9b) and the edge of a Richardson retractor introduced under the superior leaf of the dissected fascia. Upward traction places the fascia on tension, and by sharp and blunt dissection within the layers of the periuterine fascia (Fig. 9c) the fold may be elevated to give the desired exposure (Fig. 9d). This step completes that portion of the dissection peculiar to the extraperitoneal type of cesarean.

6. *Evacuation and Repair of the Uterus.*—The empty bladder is placed behind the symphysis pubis, the peritoneofascial flap is elevated by an assistant with moist gauze, and, with lateral retractors giving the necessary exposure, a low transverse cervical incision is made in the uterus.

The merits of the *low transverse cervical* incision originally proposed by one of us[10] are: (1) it lies in the course of the majority of the cervical fibers; (2) the incision is placed in the noncontractile portion of the uterus where healing is not interfered with by postpartum contractions; and (3) the incidence of rupture during subsequent pregnancies is minimal.

After an ampule of Ergotrate has been given intravenously, the infant is delivered by suitable means (manually, by vectis, or by forceps). The cord is divided and the placenta expressed. In relatively clean cases, the placenta is removed manually. The angles of the uterine incision and its midpoints are grasped with Allis forceps and the uterine cavity inspected for residual membranes which are removed if present. The patency of the cervical canal is tested to insure lochial drainage and the glove or instrument used for this purpose discarded.

The myometrium and fascia are approximated with interrupted sutures of No. 1 chromic gut, the angle and midpoint sutures being introduced first and held with clamps to facilitate insertion of the remaining sutures. The peri-uterine fascia is infolded over the first line of suture by a continuous Cushing or Lembert suture of No. 1 chromic gut.

7. *Closure of the Abdomen.*—The operative site is sponged free of blood and blood clots; there is seldom any ooze requiring attention. The bladder may be distended at this point to prove its integrity. A rubber tissue drain is placed in the retrovesical space and brought out through the lower angle of the abdominal incision. The recti muscles are loosely approximated with interrupted sutures of No. 00 chromic gut; the rectus fascia is approximated with interrupted sutures of No. 0 chromic gut; the superficial fascia is approximated with interrupted sutures of No. 000 plain gut; the skin edges are approximated with a nonabsorbable suture and the drain is fixed to the skin edge with a single suture. A sterile dressing is applied, the contractile state of the uterus is ascertained and clots are expressed from the vagina.

Summary

1. The surgical anatomy of extraperitoneal cesarean section, based on the study of forty-nine extraperitoneal operations of all major types, is presented from four interlocking points of view: (1) anatomic description, (2) planes of dissection, (3) anatomic approaches to the lower uterine segment, and (4) the technique developed from consideration of the foregoing.

2. Variations in configuration and levels of attachment of peritoneum to bladder, in the nature of the fibroareolar component of the peritoneum, in adherence of serous peritoneum to perivesical fascia, and in substance of the perivesical fascia are described. Anatomic variations of the supravesical area are emphasized. The paravesical space is described.

3. Proposed and actual planes of dissection are discussed. It is pointed out that extraperitoneal cesarean section is usually performed successfully only by employing several planes of dissection.

4. The anatomic approaches to the lower uterine segment are briefly discussed.

5. The operative technique developed as a result of the foregoing material is outlined. It consists essentially of a bilateral paravesical approach with retrovesical separation of the bladder from the lower uterine segment and subsequent dissection of the supravesical area. The easiest planes of dissection are utilized throughout.

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CONCERNING THE CHEMICAL NATURE OF MENSTRUAL TOXIN

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TWENTY-FIVE years ago, the present writer began the development of a new branch of pharmacology to which the name of phytopharmacology was given. By this is meant the study of physiologic effects of drugs and chemicals of every sort by the use of living plant-physiologic test objects. The methods employed in such work have been extensively described in previous papers.[1, 2, 3] Suffice it for the present purposes to call attention to the fact that this phytopharmacologic approach was found to be very useful in detecting and studying the various properties of chemicals contained in the blood.[4] One of the first and most interesting studies conducted in this manner was the first quantitative and experimentally reliable investigation of the so-called poison of menstruation.

An elaborate monograph on the subject was published in 1924 by the present author and Miss Dorothy Lubin,[5] in which paper it was demonstrated that a toxic substance is present in the blood, sweat, milk, and other secretions of menstrual women which can be specifically and strikingly detected by phytopharmacologic methods. Ten years later, in the paper by Macht and Davis,[6] further studies on the subject were reported and described. Another ten years later the writer wrote a third and even more comprehensive paper[7] dealing with both the historical and experimental studies on menstrual toxin by himself and other workers and containing an extensive bibliography on the subject. It was shown that menotoxin can produce definite pharmacologic effects on suitable zoological test objects, but, nevertheless, the phytopharmacologic approach was the most striking and sensitive one for studying this particular toxin. Even in the first paper by the author and Miss Lubin, the chemical nature of menotoxin was discussed and the authors stated that it is related to cholesterol and was probably some form of oxycholesterol. In the intervening twenty-five years between the beginning of these studies and the present time, menstrual toxin has been studied by various authors and different hypotheses as well as speculations have been advanced as to the chemical nature of this substance. It is the purpose of the present paper to examine the validity of these hypotheses and also to present experimental and chemical data of our own pointing to the chemistry of menstrual poison.

Method of Study

The various hypotheses advanced by different authors as to the chemical nature of menstrual toxin were put to test in two ways. In the first place, the different chemical compounds claimed to be menotoxin were tested by phytopharmacologic methods. This is an extremely useful procedure because only a very limited number of blood sera are toxic for the growth of *Lupinus albus* seedlings and, for this reason, any substance claimed to be menotoxin in nature can be conveniently put to a test by phytopharmacologic examination. A second method employs an entirely new approach to the study of the subject and involves biophysical methods which will be described later in this paper.

Experimental Critique and Evaluation of Various Theories

A. A Vasoconstrictor Substance.—One of the earliest theories advanced as to the chemical nature of menstrual poison was that of Labhardt and Hussy[8] who, on the basis of some experimental work, claimed the presence of a substance possessing vasoconstricting properties in menstrual blood. Vasoconstricting properties of normal blood serum have been described by physiologists before,[9] but in menstrual blood the authors claimed the vasoconstricting properties were greater. Could that be due to a substance in menstrual blood closely related to epinephrine? The present writer investigated the effect of adding small quantities of epinephrine to blood serum. It was shown by him that epinephrine, in contrast to ephedrine which is sometimes called vegetable-epinephrine, in saline solutions, is quite toxic for plants, but when mixed with one per cent of blood serum the weakest concentrations to which lupine roots respond were one to fifty thousand. This is much greater than the normal amount of epinephrine present in shed blood. Furthermore, it is well known that Adrenalin is such an unstable substance that, at the pH of the blood, it is rapidly oxidized. Menstrual blood, however, retains its toxicity for many days even at room temperature. These experiments, therefore, excluded the likelihood of menotoxin being related chemically to epinephrine.

B. Another hypothesis as to the nature of menotoxin was that advanced by Sieburg and Patschke,[10] Klaus,[11] and others. These writers thought that menstrual poison is closely related to *choline.* They did not, however, isolate menotoxin in chemical form and identify it with choline. On the other hand, phytopharmacologic experiments performed by Macht revealed that neither choline nor acetylcholine are toxic for lupine seedlings. It is, therefore, not probable that menotoxin is in any way related to choline chemically. We must not, however, confuse the term choline with that of *cholic acid* and its salts. They are not at all related to choline, but are chemically closely related to the bile acids. The latter have been shown by the present writer long ago to be very toxic for plants and the significance of that will be discussed later.[12]

C. Macaggi and Sivori[13] regarded menotoxin as closely related to *thyroxin* or the active principle of the thyroid gland. The present author made experiments with thyroxin solutions on the growth of lupinus seedlings and did not find it toxic for these plants in concentrations which were even greater than those present in most clinical cases of thyrotoxicosis.

D. More recently, Steinert and Papp[14] attributed the toxicity of human milk during menstruation to a reduced content in *diastatic ferments.* In other words, they tried to correlate menotoxin with diastase. The present writer made experiments on the growth of seedlings in diastatic solutions in different proportions, both in saline solution and in combination with blood serum, and did not find any toxic effects produced on the growth of the seedlings, even by quite concentrated solutions of that enzyme.

E. Another hypothesis is advanced by Ashley Montagu.[15] He holds that menstrual toxin is identical with *di-methyl-amine,* a compound described long ago by Michin. We have secured specimens of pure di-methyl-amine and studied carefully the effect of those solutions on the growth of lupinus seedlings. No toxic effects were noted, even with very concentrated solutions. It appears, therefore, that di-methyl-amine is also not likely to be the active toxic agent of menstrual blood.

F. A very interesting contribution is that of Heinrich Guthmann and K. H. Henrich.[16] These authors computed the amount of *arsenic* found in venous blood during normal conditions and during menstruation. They found that normal venous blood contains 103 gamma per cent of As. On the other hand,

menstrual blood is much richer in arsenic and contains about 320 gamma per cent of the element. This difference in the quantity of arsenic suggested that the toxicity of menstrual blood might be due to its greater arsenical content. However, this was not borne out by phytopharmacologic experiments. The present writer studied the effect of arsenical solutions with and without blood serum on the growth of lupinus seedling roots and found that concentrations even of four hundred to five hundred gamma per cent were not toxic for lupinus seedlings, whereas menstrual blood always is.

G. Italo Vandelli[17] recently called attention to another interesting finding. Normal blood always contains small quantities of *histamine* to the amount of 0.1 gamma per cent. Menstrual blood, on the other hand, was found to be much richer in histamine, containing as much as 0.36 gamma per cent. In order to ascertain whether this might account for the phytopharmacologic properties of menstrual blood, we have made experiments with solutions of histamine much stronger than the above but found that they produced no inhibitory effect on the root growth of lupinus seedlings in hydroponic solutions containing histamine.

H. Still another interesting study worth mentioning in this place is that of Eva R. Hutzler.[18] This investigator noted that menstruation produced a depressant effect on the excretion of *ascorbic acid* or vitamin C after ingestion of certain fruit. Could an excessive retention of ascorbic acid in the blood account for the toxic properties of menstrual blood? This was investigated by the present writer some years ago and studied on a large number of plants, the results of which study were analyzed statistically. It was found that ascorbic acid or vitamin C in aqueous solutions did inhibit growth of lupine seedlings but only in such concentrations as could not possibly be present in menstrual blood. Similarly, mixtures of ascorbic acid with normal blood serum were not found to be phytotoxic in concentrations greater than vitamin C occurs in menstrual blood. We may, therefore, conclude that ascorbic acid probably has no relation of chemical nature to menotoxin.

I. Finally, we wish to mention the most recent and elaborate studies by Smith[19] of Boston on a body which he called *necrosine.* This substance or mixture of substances was first described by Menkin,[20] and Smith employed his method in producing it among dogs. He claimed, for some reason not quite clear to the present writer, that menotoxin is identical with or closely related to necrosine. It was, therefore, very interesting to investigate the influence of necrosine on growth of plants. The present writer produced necrosine in dogs by the Menkin method and studied the effect of its solutions on the growth of lupine seedlings. It was found that in no case did necrosine inhibit the growth of the seedlings or produce any toxic effect. The conclusion based on phytopharmacologic studies, therefore, is that neither necrosine nor any other chemicals mentioned above agree with the properties of menstrual toxin which are exhibited by phytopharmacologic methods.

Experimental Data

A. Method.—The experimental data briefly mentioned in the above critique of various hypotheses as to the nature of menstrual toxin, and revealing their inadequacy, may now be presented in more concrete form.

The technique employed in the present author's phytopharmacologic work has been described in great detail in other papers.[21, 22] Briefly, it is performed as follows:

The toxicity of the various preparations was studied on growth of the seedlings of *Lupinus albus* by measuring carefully the elongation of the well-defined single, straight rootlets. The *Lupinus albus* is especially adapted to experiments in plant physiology and pharmacology because it can be easily germinated and the growth of the roots accurately measured. The procedure employed was as

follows: The dry seeds of *Lupinus albus* large variety were soaked overnight in tap water at the ordinary room temperature. On the following day, the swollen seeds were planted with the hilum downward in finely ground moist Sphagnum moss containing the proper amount of moisture. The seeds were then placed in the dark and kept at a constant temperature of about 20° C. On the third day after planting the seeds, the seedlings are of convenient size, the length of the roots being generally from 20 to 30 mm. The length of these roots can be accurately measured because of a definite line of demarcation indicating the border line between root and stem. After recording the exact length of a root, the seedling is placed in an upright test tube of hard glass containing a nutrient solution for plants, the seed resting on the upper edge of the tube. The solution employed was the so-called Shive[23] solution which contains calcium nitrate, magnesium sulphate, and monopotassium acid phosphate. Such a solution is prepared by mixing 10.4 c.c. of a 0.5 molar solution of calcium nitrate, 30 c.c. of a 0.5 molar solution of magnesium sulphate, and 36 c.c. of a 0.5 monopotassium phosphate solution, with distilled water sufficient to make 1 liter. The normal growth of the lupine rootlets was studied by immersing the seedlings in a mixture of normal Shive solution with an equal part of distilled water. The effect of unknown substances was studied by Macht and co-workers in other connections, by adding a definite percentage of the unknown to the distilled water and then mixing with an equal part of Shive.

In the present work, the normal growth of the seedlings was first determined by using equal parts of distilled water and the Shive solution.[23] In these extensive experiments the average growth of at least twenty and often thirty seedlings was determined for each solution used.

After all the solutions have been prepared and all the seedlings have been measured and immersed in them, the plants are placed in a low-temperature thermostat and left overnight at a constant temperature of 15° C. in the dark. The temperature throughout the experiment was followed by means of a thermograph, although variations or fluctuations in the temperature were of no significant importance, inasmuch as all the plants or seedlings, including the controls, were always kept under the same conditions. After a period of twenty-four hours and sometimes twenty hours, the seedlings are examined again. The roots are measured and the growth in various solutions is compared with the average growth in normal Shive. The sharply defined straight roots are measured at the beginning and end of every experiment, and the ratio of growth of the seedling roots in the various drug solutions is expressed as a percentage of their growth in the control solution according to the formula,

$$\text{Index of Growth} = \frac{X}{N} \times 100$$

in which N represents average growth of controls and X the average growth in the drug solution. All of the seedlings were allowed to grow for twenty-four hours in the dark at 15° C.

B. Nonphytotoxic Substances.—The action of solutions of the various compounds discussed above, which have been suggested by various authors as responsible for menotoxin or the toxic effects of menstrual blood serum, is exhibited in Table I. Here are listed the concentration of the drugs studied and the phytotoxic indices in plant-physiologic saline solutions. It will be seen that all of those bodies are either not toxic at all or are no more toxic than normal blood serum.

In the same table are also shown the effect of x-ray irradiation on such solutions in respect to their phytotoxic properties. Here it will be noted that irradiation produced either no change in toxicity or actually rendered the solu-

tions of the drugs less phytotoxic. All of these radiations were made with a Westinghouse Duocondex x-ray machine at the Sinai Hospital, Baltimore, operated on 200 kv. and a current of 20 Ma. and target distance of 50 cm., employing a composite filter of 1 mm. Al and 2 mm. Cu. The author is indebted to Dr. Marcus Ostro for his courtesies in using the above machine. The significance of these findings will be explained further on.

TABLE I. ROOT-GROWTH OF LUPINUS ALBUS SEEDLINGS IN SOLUTIONS OF SOME SUSPECTED COMPOUNDS

DRUG	CONCENTRATION	MANNER OF TREATMENT	PHYTOTOXIC INDEX IN SHIVE (PER CENT)
Choline	1:500	Untreated	97
	1:500	X-rayed with 180 r	99
Di-methyl-amine	1:25,000	Untreated	100
	1:10,000	Untreated	96
Histamine	1:5,000	Untreated	81
	1:5,000	X-rayed with 180 r	94
Thyroxin-l	1:2,000	Untreated	79
	1:2,000	X-rayed with 180 r	70
Thyroxin-d	1:2,000	Untreated	90
	1:2,000	X-rayed with 180 r	99
Arsenic	1:100,000 As	Untreated	70
(Fowler's Sol.)	1:200,000 As	Untreated	85
Diastase	1:1,000	Untreated	75
	1:2,000	Untreated	90
Necrosin	24 hours serum 1 per cent	Untreated	94
	48 hours serum 1 per cent	Untreated	62
Ascorbic acid	1:50,000	Untreated	70
Epinephrine HCl	1:40,000	Untreated	73

In Table II are given the statistical data of an experiment with ascorbic acid or vitamin C which illustrates well the reliability of phytopharmacologic experimentation when performed by a carefully trained and experienced pharmcologist acquainted with plant-physiologic methods.

TABLE II. STATISTICAL EXPERIMENT WITH ASCORBIC ACID

GROWTH OF LUPINUS SEEDLINGS IN SOLUTIONS 1:50,000			
Controls in Normal Shive Solution = 100 seedlings		Seedlings grown in vitamin C solution 1:50,000 = 100 seedlings in Shive	
Average growth of roots in 24 hours at 15° C. = 12.2 mm.		Average growth of roots in 24 hours at 15° C. = 8.5 mm.	
		Phytotoxic Index = 70 per cent	
Standard Deviation	= 2.18	Standard Deviation	= 2.49
Probable Error PE	= 0.208	Probable Error PE	= 0.237

$$\text{PE diff} = \text{PE (control)} + \text{PE (vitamin C)} = 0.315$$

$$\text{Validity or Critical Ratio} = \frac{D}{\text{PE diff}} = 11.7$$

Concerning the Relationship of Menotoxin to Cholesterol

Even in the earlier monograph of Macht and Lubin some of the physical and chemical properties of menotoxin were described by those authors. It was shown that exposure to heat does not change the toxicity of menstrual blood serum. Neither do drying and freezing destroy the phytotoxic properties of such

bloods. It was actually possible to distinguish between blood stains on cotton or linen fabric made by normal and menstrual bloods, respectively.[24] Menotoxin is not destroyed by mild acids or alkalies. It does not pass, however, through dialyzing membranes. It is soluble in alcohol, chloroform, ether, and acetone. These various chemical properties of the toxin, together with numerous pharmacologic tests produced both on animal and vegetable living tissues led the authors to suspect a close relationship between menotoxin and cholesterin or more strictly speaking, oxycholesterin.

Thus, it was discovered that wherever found in the human body, whether in the skin fat or in the vernix caseosa or elsewhere, even weak solutions of oxycholesterin in plant-physiologic media markedly inhibited the growth of *Lupinus albus* seedlings. Unna and Golodetz[25] have shown that the human skin is rich in fats containing considerable quantities of cholesterol and cholesterol derivatives. Furthermore, comedones and sebaceous glands of the face, and fingernails have proved to be rich in cholesterol derivatives. Phytopharmacologic experiments performed by the writer revealed that extracts of all these were toxic for *Lupinus albus* seedlings. Other poisons of animal origin, such as the toad poison, *bufagin*, of Abel and Macht,[26] had been found by the latter to be very poisonous for plant growth. This toad poison, as well as others later studied by Chen,[27] are all derivatives of cholesterol. Perhaps the most striking single experimental proof supporting the original oxycholesterol theory was the finding by Rahn,[28] Barnes,[29] Ferguson,[30] and Christiansen[31] that inhibitory effects on yeast similar to those the first writer had observed in his radiologic tests on menstruating women were produced by cholesterol itself. Further support is lent the cholesterol or oxycholesterol hypothesis by the fact that recent chemical studies on the structure of the sex hormones in general and of ovarian hormones in particular have disclosed their intimate relationship in chemical structure to cholesterin. The findings made by Macht and his associates on the interrelation of menotoxin and bile salts also support this view.

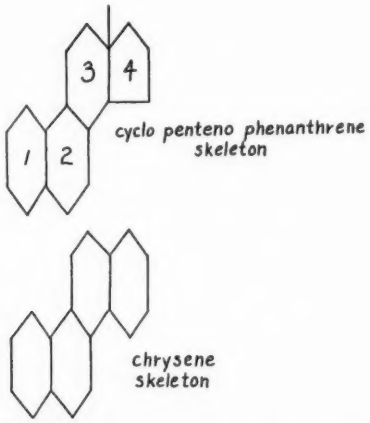

Fig. 1.—Skeletons of the chemical structure of the principal steroids.

Inasmuch as it is now known that all of the sex hormones, both male and female, belong to the steroid group of chemicals, it was deemed worth while to investigate, as far as possible, the action of solutions of ovarian hormones on the growth of plants. Special studies were made by the present author on the effects of estrone and progesterone on the root growth of *Lupinus albus* seedlings

by the methods already described above. Fortunately, these insoluble substances are sufficiently soluble in plant-physiologic saline to exert definite effects on the growth of the seedlings. Briefly, the method employed was to dissolve the hormones in strong ethyl alcohol and, using this solution as a starting point, to dilute it to very low concentrations suitable for the growth of seedlings without danger of harming the plants by the dilute alcohol. It was found that very weak solutions of estrone actually produced stimulation in the growth of the seedlings but when slightly stronger solutions were employed they were definitely phytotoxic. On the other hand, progesterone even in very extremely dilute concentrations exerted an inhibitory phytotoxic influence on the lupine seedlings.[32] These effects are shown in Table III.

TABLE III. TABLE OF ROOT GROWTHS

ESTRONE – 1:200,000		PROGESTERONE – 1:200,000	
PHYTOTOXIC INDEX (PER CENT)	NO. OF ROWS	PHYTOTOXIC INDEX (PER CENT)	NO. OF ROWS
120	3	85	3
112	3	78	3
136	3	73	3
120	2	69	2
135	3	84	3
120	2	69	2
101	2	60	2
116	2	78	2
108	2	77	2
103	1	88	1
108	3	77	3
111	3	66	3
116	2	78	2
Average 117	31	Average 75	31

Recent chemical studies support this view for the findings of the present writer and his associates regarding the chemical structure of menotoxin and those of Rahn, Barnes, Ferguson and other investigators indicate its probable close relationship to oxycholesterol. It is now known that the ovarian hormones also are closely related to that substance, the investigations of Mandelshtam, Tschaikowsky, and Bondarenko[33] supplying further evidence in this connection. Studying the chemical nature of menotoxin by phytopharmacologic methods, these investigators also experimented on the effect of folliculin and the lipoid portions of the ovaries on plant growth and concluded that menstrual poison is closely related to the ovarian sex hormones. The present writer found that while crystalline estrone solution has a tendency to stimulate root growth of *Lupinus albus* seedlings, crystalline progesterone definitely inhibits it. The findings of Macht and his associates on the interrelation of menotoxin and bile salts also tend to support the view that menotoxin is closely allied to cholesterol. It is remarkable that such divergent substances as the carcinogenic chemicals, digitaloid drugs, toad poisons, sex hormones, ergosterol, calciferols and the group of compounds included under vitamin D, and menotoxin are all closely related chemically. All these are derivatives of phenanthrene and possess a structure not far removed from that of oxycholesterol. Such a relationship does not preclude the possibility of menotoxin's being much more toxic than the ovarian hormones, as pharmacology abounds in striking examples of chemicals closely related in structure yet exhibiting diametrically opposite physiologic and toxicologic properties, due to slight alterations in the relative position of some of their atoms.

Biophysical Evidence

Mention has already been made by the author that the phytotoxic properties of menstrual toxin can be readily distinguished from those of pernicious anemia by their response to ultraviolet rays.[34] It was found that short exposures of pernicious anemia serum to the rays of a mercury vapor lamp were followed by a complete loss of toxicity. On the other hand, when menstrual serum was exposed to such rays, no change in toxicity occurred and occasionally the serum became even more phytotoxic.

In the past few years, Macht and Ostro, experimenting on the pharmacologic effects of x-rays, discovered that exposure of pernicious anemia serum, the serum of pemphigus, and the sera from various psychotic patients were rapidly detoxified or rendered less phytotoxic by irradiation with short x-rays filtered through a composite filter of 1 mm. Al and 2 mm. Cu. To their surprise, it was found that when menstrual serum was exposed to the same rays the phytotoxic properties were not destroyed by 100 r. or more and, in fact, they were usually enhanced. Table IV illustrates such findings made in twelve experiments.

This interesting discovery suggested an examination of other steroid compounds in respect to their phytotoxic properties before and after exposure to short or hard x-rays. A considerable number of such compounds were collected and examined. Most of these are quite insoluble in water but fortunately they are soluble in sufficient amounts to exert phytopharmacologic effects. Table V gives a list of the compounds examined and also their toxicity for the root growth of *Lupinus albus* seedlings before and after irradiation with roentgen rays. Table VI shows how even very weak solutions of estrone and progesterone are rendered more toxic by irradiation. It will be noted that, in every case, the irradiated specimens were much more phytotoxic than the nonradiated ones. It is interesting to note also that this group of steroids include important substances belonging to diverse pharmacologic groups. Thus, it includes various cardiac glucosides; it includes some of the best-known vitamins, such as ergosterol and calciferol; it includes the toad poisons; and finally, it includes the large group of sex hormones which have already been isolated in pure chemical form up to the present time. The general structure of these steroid compounds is shown in Fig. 1. They are all related to phenanthrene or chrysene and a more intimate chemical structure can be found in the valuable monograph on steroid compounds by Sobotka.[35] It is always dangerous to make general statements in any kind of scientific researches and especially so in pharmacologic work which aims at tracing relationships between chemical structure and physiologic action, but it is certainly remarkable to find that all of the steroid compounds so far studied by the present author in respect to their phytotoxic action are rendered more potent by roentgen irradiation. It is, therefore, perhaps, permissible to regard this remarkable pharmacologic property as a further corroboration of the author's hypothesis that menotoxin is closely allied to cholesterol on the one hand and to the sex hormones on the other hand and is chemically to be classed with the steroid group of chemical compounds which play such a very important role in biochemistry. Thus we see that, in the light of twenty-five years of experimentation and experiences since the first publication of the monograph on menotoxin by Macht and Lubin, the original contention that this toxin is closely related to the phenanthrene derivatives, cholesterol and oxycholesterol, has been largely corroborated; and, while it is a separate toxic entity, it is probably closely related to the female sex hormones which are also now known to be natural products of phenanthrene and belong structurally to the steroid class of chemical compounds.

TABLE IV. MENSTRUAL SERA

NO.	PHYTOTOXIC INDEX NONRADIATED (PER CENT)	PHYTOTOXIC INDEX AFTER RADIATION THROUGH 1 MM. AL., 2 MM. CU., 108 R. (PER CENT)
1	60	54
2	50	57
3	50	54
4	68	69
5	47	46
6	57	49
7	52	46
8	47	44
9	48	46
10	48	48
11	48	20
12	34	19
Average:	60.9	Average: 55.2

TABLE V. STEROID DRUGS

ROOT-GROWTH OF LUPINUS ALBUS SEEDLINGS IN IRRADIATED AND NONIRRADIATED SOLUTION				
		PHYTOTOXIC INDEX		
DRUG	CONCENTRATION	NOT RADIATED (PER CENT)	X-RAYED THROUGH 1 MM. AL. R.	2 MM. CU. (PER CENT)
Digitoxin (Winthrop)	1:100,000 in 1% Alc Shive	81	180	77
Digitaline Nativelle	1:25,000	91	180	83
Digitoxin (Wyeth)	1:100,000 in 1% Alc Shive	62	90	54
Digitoxin (Wyeth)	1:100,000 in 1% Alc Shive	62	180	47
Digitoxin (Wyeth)	1:100,000 in 1% Alc Shive	62	270	38
Lanatoside (Cedilanid)	1:100,000 in 1% Alc Shive	77	108	59
Cubain	1:50,000 in 1% Alc Shive	85	180	66
Cholesterol	Sat. Sol. in 1% Alc Shive	85	108	76
Ergosterol	Sat. Sol. in 1% Alc Shive	71	108	58
Calciferol	Sat. Sol. in 1% Alc Shive	88	180	72
Sodium cholate	1:5000	78	180	57
Testosterone	Sat. Sol. in 1% Alc Shive	80	180	68
De-hydro-iso-androsterone	Sat. Sol. in 1% Alc Shive	65	180	50
Alpha estradiol	Sat. Sol. in 1% Alc Shive	80	144	51
Pregneninolone	Sat. Sol. in 1% Alc Shive	71	180	51
Di-hydro-tachysterol	Sat. Sol. in 1% Alc Shive	68	108	42
Bufagin (B-marinus)	Sat. Sol. in 1% Alc Shive	87	144	71
Estrone (crystalline)	1:100,000 in 1% Alc Shive	98	180	75
Progesterone (crystalline)	1:100,000 in 1% Alc Shive	80	180	63

TABLE VI. ROOT-GROWTH IN ESTRONE AND PROGESTERONE

CRYSTALLINE ESTRONE		CRYSTALLINE PROGESTERONE	
SOLUTION	INDEX OF GROWTH (PER CENT)	SOLUTION	INDEX OF GROWTH (PER CENT)
Saturated aqueous solution in Shive 13 experiments, 31 rows of 10 plants each	117	Saturated aqueous solution in Shive 13 experiments, 31 rows of 10 plants each	75
Solution in 1% Alc Shive 1:100,000		Solution in 1% Alc Shive 1:100,000	
Nonradiated	98	Nonradiated	75
X-rayed 180 r.	75	X-rayed 180 r.	60

Summary

1. Various theories held as to the nature of menstrual toxin have been described.

2. These have been put to test by phytopharmacologic experiments and found inconclusive.

3. All evidence gathered from the author's own experimental investigations, as well as data gathered from literature, points to menotoxin's being closely related pharmacologically and chemically to cholesterol and oxycholesterol on the one hand, and to the female sex hormones on the other; all of these compounds are natural products of phenanthrene, and belong to the important class of organic compounds known as steroids.

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MALIGNANT TUMORS OF THE UTERINE FUNDUS SUBSEQUENT TO IRRADIATION FOR BENIGN PELVIC CONDITIONS

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EXPOSURE of the female genital organs to radiant energy in the form of x-rays or radium emanations may not be as innocuous as it has long been believed to be. At least 21 of the 270 patients who have been treated for malignant tumors of the uterine fundus on the gynecologic service of the Roosevelt Hospital have had previous pelvic irradiation for benign conditions. It is the purpose of this report to review these cases and to assess the possible role of radiotherapy in the subsequent development of uterine cancer.

This problem assumes practical clinical importance in view of the frequency with which many gynecologists use radium and roentgen therapy for uterine myomas and benign uterine bleeding (Norris and Behney, 1936; Crossen and Crossen, 1947; Schmitz and Towne, 1947; Lockwood, Smith, and Walker, 1947). Approximately 13 per cent of women approaching the end of their menstrual life suffer from excessive flow (Corscaden, Fertig, and Gusberg, 1946). Randall (1945) has shown that women with menorrhagia immediately preceding the menopause have a peculiar predisposition to the later development of endometrial cancer. This thesis has been extended by Corscaden, Fertig, and Gusberg, whose calculations show that 9.6 per cent of women who experience excessive bleeding at the climacteric are destined to develop cancer of the endometrium before the age of 80. This is more than 3 times the expected incidence. Werner (1925), Taylor (1932), Macfarlane (1932), and Randall (1945) have suggested that pelvic irradiation may serve as a prophylactic measure against the development of corpus cancer in such patients. Others, however, believe that radiant energy may stimulate cancer formation in the uterus. Statistical evidence is lacking to support or refute these views. It has been difficult to dissociate a possible carcinogenic effect of the rays from an inherent susceptibility which patients so treated may have to the disease.

The following is a chronological summary, probably incomplete, of the published reports of cases in which fundal cancer has developed subsequent to the treatment of women with radium or x-rays for benign pelvic conditions.*

1. Werner (1925) reported 3 cases in which carcinoma of the corpus occurred in women aged 36 to 47 years, between eight months and seven years after treatment with x-rays. These were among a total of 2,680 patients similarly treated.

2. Vogt (1926) reported 3 cases of fundal carcinoma after x-ray castration (one patient having received radium also), and 3 cases of sarcoma of the uterus after exposure to x-rays. His review of the literature, including his own patients, showed 30 cases of uterine carcinoma and 7 cases of uterine sarcoma following previous x-ray therapy.

3. Bland (1929) treated a patient, aged 56 years, with 2,400 mg. hr. of intrauterine radium for a myoma. Three years later she was found to have an early endometrial cancer.

*Forty additional cases have been reported recently by Toffe, H. H., Eckman, P. F., and Wells, A. H., Minnesota Med. **31**: 789, 1948, and Smith, F. R., and Bowden, L.: Am. J. Roentgenol. **59**: 796, 1948.

4. Stacy (1929) found 2 patients who had been treated with radium for fibroids, two and seven years previously, respectively, among 333 cases of corpus cancer at the Mayo Clinic.

5. Macfarlane (1932) added a case in which carcinoma developed in a 60-year-old woman, fifteen years after an x-ray menopause for a uterine myoma.

6. Martindale (1933) reported 2 cases of fundal carcinoma which developed seven and three years, respectively, after induction of the menopause by means of x-ray irradiation. In a third case, sarcoma was found four years after irradiation of a fibroid uterus.

7. Schmitz (1934) discovered 9 carcinomas of the uterus among a group of 433 women who had been treated previously with x-rays or radium for uterine hemorrhage resulting from benign lesions.

8. Hoffmann (1934) recorded a case of fundal carcinoma which developed three years after an x-ray castration.

9. Fournier (1935) reported a case in which corpus cancer developed in a patient aged 53 years, ten years after a radiotherapeutic menopause induced by x-rays and radium.

10. Norris and Behney (1936) observed 11 pelvic carcinomas (organ not stated) among 1,006 patients who had been treated with intrauterine radium two or more years previously for functional bleeding or uterine myomas.

11. Pemberton (1936), in discussing the paper of Norris and Behney, stated that of 4 pelvic tumors which developed among 425 women who had been treated with radium two or more years before for functional bleeding, at least 1 was an endometrial cancer. This was diagnosed 11 years after the irradiation.

12. Strachan (1936) added 2 more cases. The first was that of a girl who had had 3 curettages and finally intrauterine radium (2,400 mg. hr.) at the age of 24 years, for bleeding associated with endometrial hyperplasia. Three years of amenorrhea followed. Four years later a papillary carcinoma of the endometrium was discovered. The second patient, a woman 45 years of age, was given intrauterine radium (2,400 mg. hr.) for climacteric bleeding. Four years later she was found to have carcinoma of the fundus.

13. Malpas (1937) recorded another case of corpus cancer after a radium menopause. He also cited a personal communication from Essen-Möller, who observed 6 cases of endometrial carcinoma after the same treatment and accordingly abandoned it.

14. Mazzola (1938) reported the case of a young woman who had 3 radium treatments (1,200 mg. hr. total) and 2 x-ray treatments (650 r. total) for recurrent endometrial hyperplasia over a period of nine years and was found to have an adenocarcinoma of the endometrium 3 years later.

15. Luker (1939) treated his patient, aged 51, with 1,800 mg. hr. of radium because of climacteric bleeding (curettings showed secretory endometrium). After three years' amenorrhea, she was found to have a carcinoma of the fundus.

16. McDonald, Broders, and Counseller (1940), in their study of 20 cases of sarcoma of the endometrium, found that 2 of the patients had had their menopause induced previously by radium or x-rays.

17. Costolow (1941) reported 3 patients with carcinoma of the corpus among a group of 1,009 patients treated with radiation for myoma and followed for two and one half to twelve and one half years.

18. Vogt (1941) added another case of endometrial carcinoma which developed two years after the treatment of a 59-year-old woman with 1,000 mg. hr. of radium because of a benign polyp of the endometrium.

19. Scheffey (1942), from among a total of 124 cases of fundal neoplasms, reported 13 cases, including 1 myosarcoma, in which the patients had received previous radiation therapy for presumably benign conditions. Most of the previously irradiated patients, however, probably had cancer of the uterus at the time of their original treatment.

20. Burnam (1942), in discussing Scheffey's paper, reported 6 malignant tumors of the fundus, including one sarcoma, which developed among 625 patients treated with intrauterine radium for post menopausal bleeding of benign origin.

21. Randall (1945) observed 4 cases in which adenocarcinoma of the endometrium was recognized a year or more after the patient had received 1,000 to 1,800 mg. hr. of intrauterine radium.

22. Corscaden, Fertig, and Gusberg (1946) reported 9 malignant lesions of the endometrium, including 1 adenosarcoma, among 958 patients who were followed an average of 6.7 years after a radiotherapeutic menopause.

23. Taylor and Becker (1947) reported that 4.97 per cent of a group of 531 patients with carcinoma of the corpus had had an artificially induced menopause.

24. Tyrone (1947), in an analysis of 436 hysterectomies, mentioned 7 cases in which cancer of the endometrium developed several years following radium therapy for benign conditions.

25. Rongy (1947) reported one endometrial cancer which appeared eleven years after x-ray treatment of a woman, aged 32 years, with bleeding of benign origin; and another which was discovered five years after 2 applications of intrauterine radium.

26. Kamperman (1947) added 2 more cases of corpus carcinoma in women who had had an x-ray menopause thirteen and twenty years previously.

Present Study

Records of the gynecologic service of the Roosevelt Hospital from 1915 to June 1, 1947, contain 270 cases of primary malignant tumor of the uterine fundus. We have examined the histories of all these patients in an effort to determine the number who had had pelvic irradiation before the diagnosis of uterine cancer was made. Details of previous treatment and diagnosis in other hospitals were obtained whenever possible. All available curettings obtained prior to the diagnosis of the malignant condition were re-examined, and when the original blocks were still available additional sections were cut and studied. In several instances the original diagnosis of hyperplasia of the endometrium was changed to adenocarcinoma, and in 2 other cases carcinoma was discovered in the resectioned curettings which had been diagnosed originally as benign (Taylor, 1932). After excluding these cases in which unrecognized cancer was present at the time of the original treatment, 21 remained in which a malignant tumor of the corpus was discovered subsequent to pelvic irradiation for presumably benign conditions. This represents an incidence of approximately 8 per cent among our patients with fundal cancers.

The cases are summarized in Table I. The ages of the patients at the time of diagnosis of the malignant tumor ranged from 37 to 74 years, averaging 58 years. This does not differ significantly from the average age of patients with carcinoma of the endometrium as reported in the literature and as we have found among our own patients with this disease (56.6 years). Sixteen of the patients had been treated with radium, 4 with x-ray, and 1 with both. The uterine cavity was the site of radium application in all cases but one. The average radium dose in the 11 cases where this could be ascertained was 1,006 mg. hr., ranging from 350 to 1,500. Diagnosis of the curettings obtained at the time of the original radium treatment was available in 12 cases. Endometrial hyperplasia was present in at least 6 of these. Uterine myomas were the indication for irradiation in 7 cases. The time interval between radiotherapy and recognition of the malignant tumor averaged 8.3 years, varying from eight months to nineteen years.

The tumors have been divided into three main histologic groups. Among the 20 lesions of which the exact histologic type could be determined, 11 were adenocarcinomas, 3 were adenoacanthomas, and 6 contained sarcomatous elements. The last group included 2 myosarcomas, 1 carcinosarcoma, and 3 mixed mesodermal tumors which contained epithelium, connective tissue, and cartilage. The main clinical features of several illustrative cases are presented in the following brief abstracts.

TABLE I. FUNDAL NEOPLASMS IN WOMEN TREATED PREVIOUSLY WITH PELVIC IRRADIATION

CASE	AGE	IRRADIATION	ORIGINAL DIAGNOSIS	INTERVAL	TUMOR TYPE
1	57	Radium: 1,500*	Hyperplasia	5 years	adenocarcinoma
2	65	Radium: ?	"Non-malignant"	4 years	adenocarcinoma
3	61	Radium: ? 2 applications	Postmenopausal bleeding	1 ½ years	adenocarcinoma
4	56	X-ray	Menorrhagia	7 years	adenocarcinoma
5	60	Radium: ?	Myoma	Unknown	adenocarcinoma
6	68	X-ray: 2 series	Unknown	10 years 5 years	adenocarcinoma
7	65	Radium: 1,000	Hyperplasia	4 years	adenocarcinoma
8	55	Radium: 1,216	Hyperplasia	19 years	adenocarcinoma
9	54	X-ray	Myoma	12 years	adenocarcinoma
10	37	Radium: 800	Hyperplasia	16 years	adenocarcinoma
11	40	Radium: ? X-ray	Myoma	8 months	adenocarcinoma
12	74	Radium: 400	Hyperplasia	5 years	adenoacanthoma
13	52	Radium: 350	Urethral caruncle	5 years	adenoacanthoma
14	56	Radium: 600	Hyperplasia	13 years	adenoacanthoma
15	52	X-ray	Myoma	7 years	myosarcoma
16	67	Radium: ? Radium: 1,200	Myoma Polyp	5 years 1 year	myosarcoma
17	54	Radium: ?	Myoma	10 years	carcinosarcoma
18	61	Radium: 1,200	"Benign"	12 ½ years	mixed tumor
19	55	Radium: ?	Myoma	14 years	mixed tumor
20	64	Radium: ?	Menopausal bleeding	9 years	mixed tumor
21	59	Radium: 1,000	Polyp	6 ½ years	not determined

*Radium dosage is expressed in milligram hours.

CASE 14.—V. M. (R. H. No. 43066), an Irish widow, 43 years of age, was admitted to the gynecologic service of the Roosevelt Hospital for the first time on Dec. 7, 1933, complaining of menopausal symptoms and of vaginal bleeding of three weeks' duration. Her pelvic organs seemed grossly normal. Curettage was performed on Dec. 9, 1933, at which time 50 mg. of radium was inserted into the uterine cavity and allowed to remain for 12 hours, giving a total dose of 600 mg. hr. Histologically, the curettings showed endometrial hyperplasia, this diagnosis being corroborated later by study of sections cut from different levels of the block. The patient remained well until March 21, 1947, 13 years later, when she was re-admitted to the hospital at age of 56 because of a bloody vaginal discharge which began one week previously. Her uterus felt boggy and about twice normal size. Curettage on March 22 yielded a large amount of necrotic tissue, sections of which showed adenoacanthoma (Fig. 1). Total hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were performed on March 24, 1947. The uterine cavity was filled with a foul, polypoid, necrotic tumor, with extension through about half the thickness of the myometrium.

CASE 17.*—D. L. (R. H. No. 24318 and No. 40187), a widowed white woman with one child, had a radium menopause induced at another hospital in 1936, at age 44, because of menorrhagia associated with uterine myomas. Re-examination of the curettings obtained at this time showed normal secretory endometrium. The dose of radium could not be determined but the patient had no further bleeding until 1940. Bleeding of varying severity then began to recur at irregular intervals until January, 1946, when she was hospitalized elsewhere. The uterus was described as semicystic and enlarged to the size of a 3 months' pregnancy. On Jan. 25, 1946, subtotal hysterectomy was performed. A necrotic semigelatinous mass filled the endometrial cavity. Microscopically, the tumor consisted of atypical glandular epithelium which had invaded the myometrium. The cells and nuclei varied in size and staining characteristics and many mitotic figures were present. The stroma contained cells of irregular size

*This case appears to be identical with one of the two cases of carcinosarcoma of the uterus reported by Lisa, S. R., Hartman, H., Bayer, I., and Bonar, L. D.: Ann. Surg. 127: 738, 1948.

Fig. 1.—Case 14. Adenoacanthoma of endometrium in patient aged 56 years, thirteen years after treatment with intrauterine radium for endometrial hyperplasia.

Fig. 2.—Case 17. Carcinosarcoma of fundus in patient aged 54 years, ten years after treatment with intrauterine radium for myoma. Section shows glandular elements of tumor.

and shape, including occasional giant cells. A diagnosis of carcinosarcoma was made by the 3 pathologists who examined the sections (Figs. 2 and 3). Because of her poor cooperation, the patient received only an incomplete course of deep x-ray therapy to the pelvis postoperatively. Vaginal bleeding soon recurred and she was admitted to the Roosevelt Hospital with this chief complaint on Oct. 6, 1946. A large sloughing tumor filled the upper vagina and lower pelvis, completely replacing the cervix. Biopsy of the tumor on several occasions confirmed the earlier diagnosis of carcinosarcoma.

CASE 15.—P. G. (R. H. No. 21167 and No. 341099), a 52-year-old married Negress with one child, was admitted to the hospital on Dec. 6, 1933, because of a pelvic tumor and pain in the back and legs. Seven years previously she had received elsewhere a cycle of eight x-ray treatments to the pelvis because of this tumor and had been amenorrheic since. Her uterus was irregularly enlarged by a mass about 8 cm. in diameter. On December 28, subtotal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were performed. The anterior surface of the fundus contained a degenerated myoma, section of which showed large irregular spindle cells with atypical nuclei and mitotic figures (Fig. 4). This tumor was diagnosed as a myosarcoma. The uterus also contained several smaller subserous and intramural benign myomas. Sections of the adnexa were negative. On Feb. 1, 1934, eight 5 mg. needles of radium were inserted into the cervical tissue about the external os, where they were allowed to remain for forty-eight hours, giving a total dose of 1,920 mg. hr. Despite high voltage x-ray therapy, her abdominal pain and backache grew worse and she was readmitted on March 16. A large nodular mass was now palpable in the epigastrium. Roentgenogram of the chest showed several rounded shadows in the lower half of the right lung field which were described as characteristic of sarcomatous metastases. Soon after admission, both legs became paralyzed. The patient grew weaker rapidly and died in uremia on April 20, 1934. At autopsy, sarcomatous metastases were found in the lungs, heart, liver, pancreas, intestines, and abdominal lymph nodes.

CASE 16.—E. S. (R. H. No. 14733 and No. 15759), an English widow of 67 years, was admitted to the hospital on Sept. 17, 1926, because of intermittent vaginal discharge, first watery, then bloody, of a year's duration. She had had a myomectomy elsewhere twenty-two years before, at age 45, at about the time of her menopause. Four years before admission, a submucous hyalinized uterine myoma was removed vaginally at the Memorial Hospital and intrauterine radium was administered, but no details concerning dosage are available. On admission, several polypoid bleeding masses were protruding from a normal appearing cervix. Neither the fundus nor adnexa were palpable. Curettage was performed on Sept. 27, 1926, and 50 mg. of radium were inserted into the uterine cavity for twenty-four hours, giving a total radium dose of 1,200 mg. hr. Microscopically, the curetted tissue presented the typical appearance of a benign endocervical polyp. About a year later, vaginal bleeding recommenced; the patient was readmitted to the hospital on Nov. 1, 1927. The cervix was now dilated by two large purple tumors which were avulsed. Microscopic sections showed a myosarcoma with myxomatous degeneration. The preserved areas of the tumor, which were abundantly supplied with capillaries, contained spindle-shaped cells with large hyperchromatic nuclei and many mitotic figures (Fig. 5).

CASE 18.—F. B. (R. H. No. 18480), the mother of four children, had been treated with 1,200 mg. hr. of intrauterine radium by Dr. James A. Corscaden on Jan. 18, 1918, following a curettage in her home. The curettings were reported as "benign" but no detailed description was recorded. The patient was admitted to the Roosevelt Hospital as a private patient of Dr. Howard C. Taylor on Sept. 17, 1930, at age 61, complaining of backache, lower abdominal discomfort, and cystitis. The uterus reached to the level of the umbilicus. On the following day, total hysterectomy and bilateral salpingo-oophorectomy were performed. The uterine cavity was distended by what appeared to be a submucous myoma, which measured 15 by 12 by 10 cm. Histologically, the tumor was classified as a malignant mixed tumor (adenosarcoma) of the uterus. Numerous islands of cartilage were present, surrounded by large vesicular cells and occasional giant cells (Fig. 6). Other areas contained

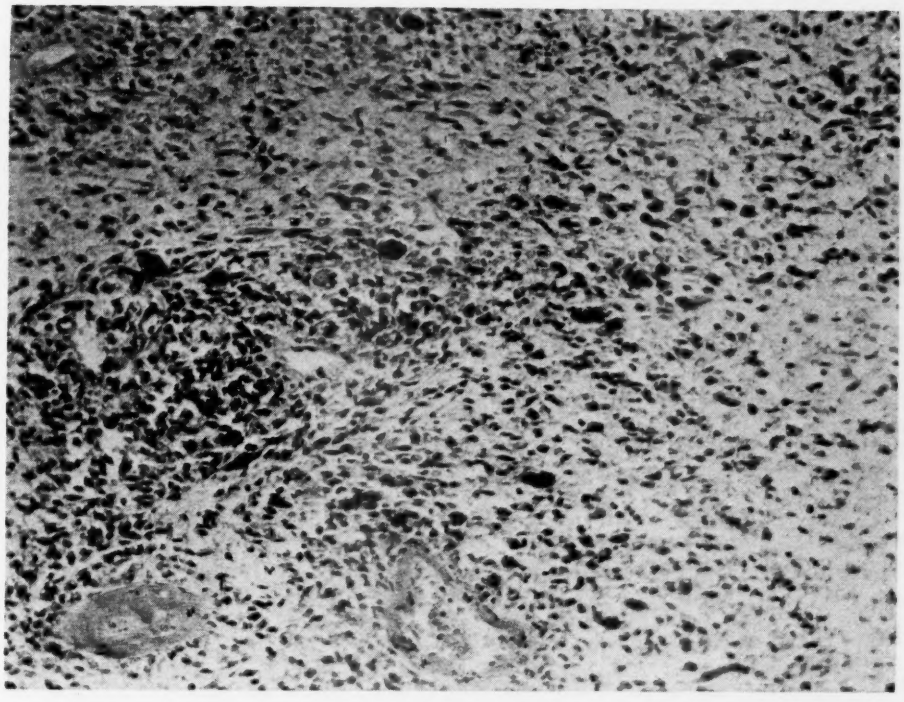

Fig. 3.—Same as Fig. 2, showing sarcomatous pattern. Note giant cells.

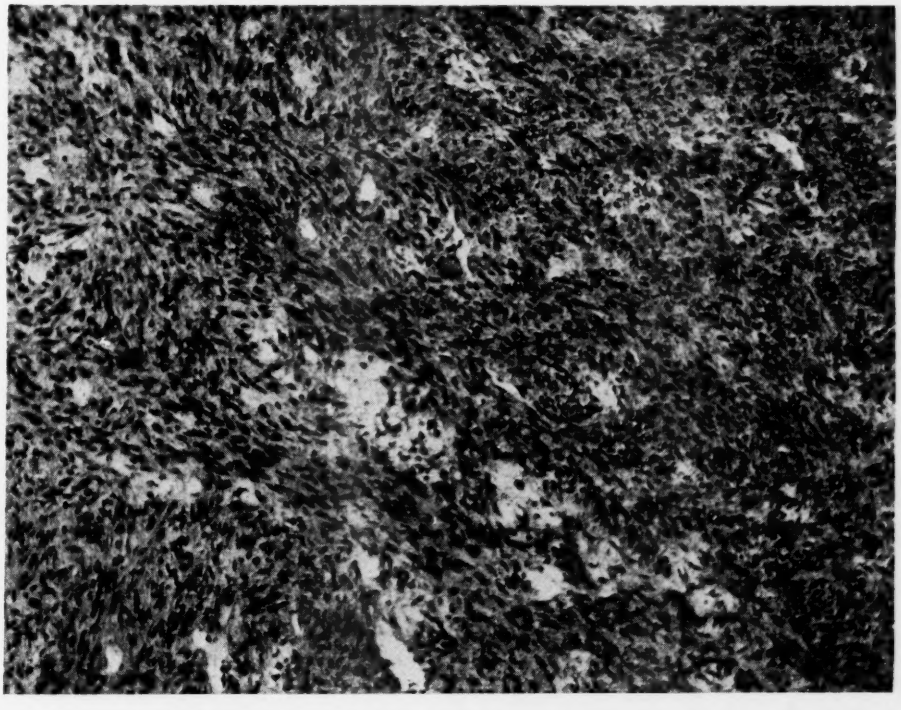

Fig. 4.—Case 15. Myosarcoma of uterus in patient aged 52 years, seven years after x-ray irradiation of myoma.

islands of high columnar epithelium with small darkly staining nuclei. This case was included in the study of Corscaden, Fertig, and Gusberg (1946).

Comment

The important clinical question to which an answer is sought is whether pelvic irradiation influences the subsequent development of neoplastic disease of the uterine fundus. Others have studied this problem by observing the incidence of fundal cancer in a series of patients previously treated for benign pelvic conditions. Corscaden, Fertig, and Gusberg found the number of patients who developed the disease in such a series to be 3.4 times as large as the number expected in a random population of the same age distribution. They attributed this disparity, however, not primarily to the irradiation, but rather to the original condition for which the treatment was given; that is, pathological uterine bleeding, often associated with endometrial hyperplasia. In the present series also, hyperplasia was present at the time of original treatment in at least 6 of the 12 cases in which the diagnosis of the curettings was available. This observation offers some support to the claim for an association between hyperplasia and carcinoma of the endometrium (Taylor, 1932; Novak and Yui, 1936).

Another observation, subject to the same difference of interpretation, concerns the relative incidence of previous pelvic radiotherapy among patients who subsequently developed corpus cancer and those with cervical cancer. In the Roosevelt Hospital, carcinoma of the cervix has been slightly more than twice as common as fundal neoplasms. Only two patients with cervical cancer, however, out of a total of 622, gave a history of a previous radiotherapeutic menopause, an incidence of 0.3 per cent. This figure contrasts with the 8 per cent incidence of previous pelvic radiotherapy among 270 women with neoplasms of the corpus. In other words, previous irradiation of the uterus was 27 times as common among patients with corpus cancer as among those with cervical cancer. This finding is in general agreement with the experience of others. Did the radiant energy bear any causal relationship to the later development of the fundal neoplasms?

Those who would answer this question in the negative call attention to the low incidence of uterine cancer among large series of women who have had pelvic irradiation for benign conditions. This approach, although valid in principle, is vitiated by the incompleteness of the follow-ups and by their comparatively short durations. Even in the study of Corscaden, Fertig, and Gusberg, for example, where a high incidence of cancer was found, only 958 of their 1,108 patients were followed, and in 359 (37 per cent) the follow-up period was less than two years. In the present series, the average latent period between radiotherapy and recognition of the fundal tumor was 8.3 years, 19 years elapsing in one case.

Martland, in 1931, reported his detailed study of the cases of osteogenic sarcoma that had occurred among radium dial painters. In the same paper he called attention to the high incidence of primary carcinoma of the lung in miners working with radioactive ores, as in the cobalt mines of Schneeberg and the pitchblende mines of Joachimsthal. It is a well-known clinical fact that irradiation of certain tissuess, such as the skin, may cause hyperplasia of the epithelium

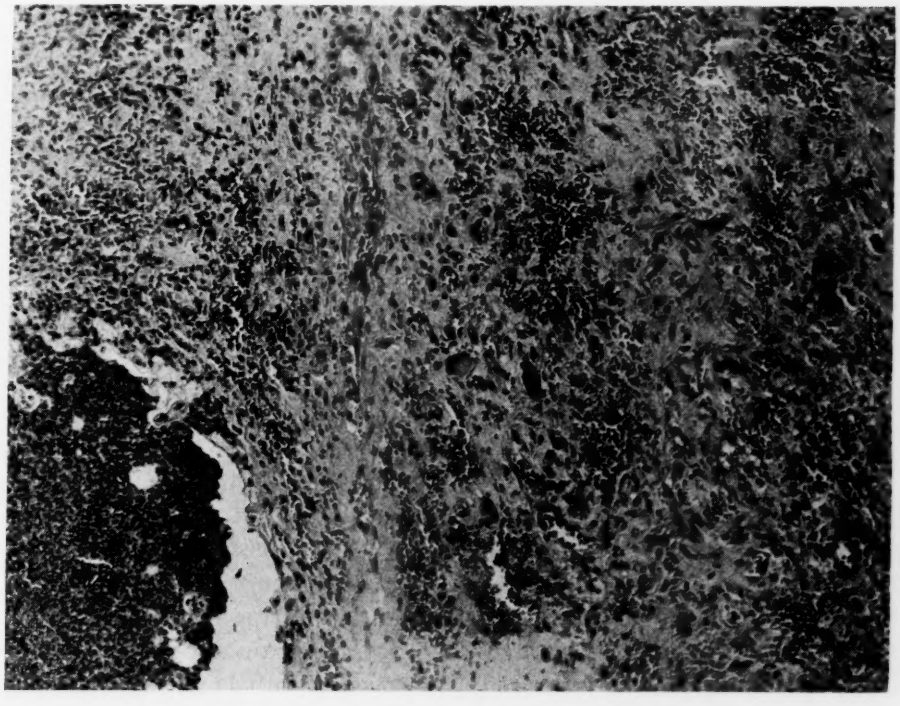

Fig. 5.—Case 16. Myosarcoma of uterus in patient aged 67 years, five years after treatment with intrauterine radium for a myoma and one year after treatment with intrauterine radium for an endocervical polyp.

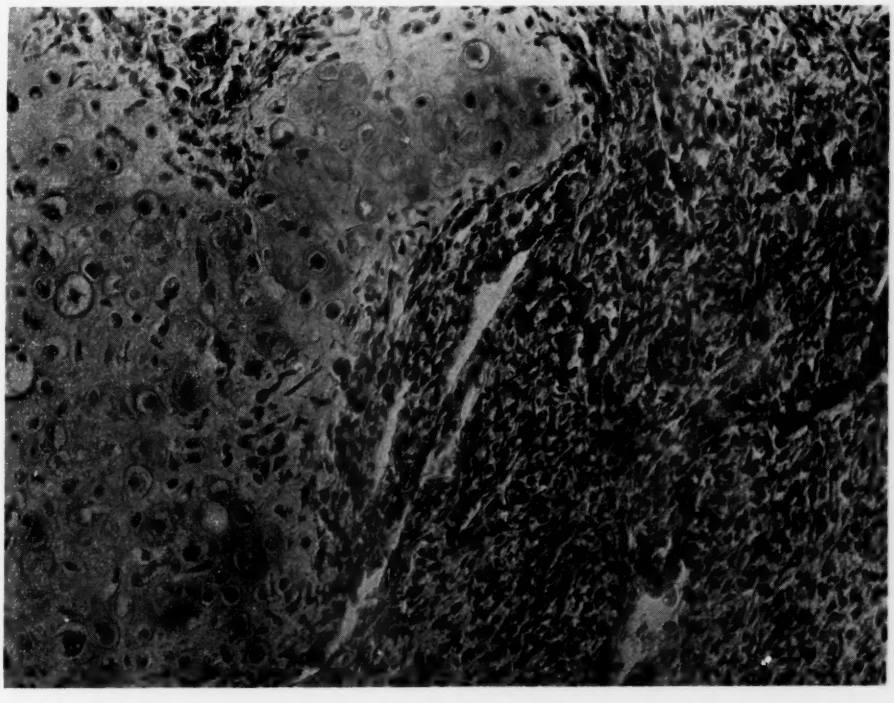

Fig. 6.—Case 18. Mesodermal mixed tumor (adenosarcoma) of the uterus in patient aged 61 years, twelve and one-half years after treatment with intrauterine radium. Note cartilage in tumor.

and in some cases, especially if the irradiation is oft repeated, leads to malignant transformation. Several case reports which clearly incriminate roentgen or gamma rays as carcinogenic agents for skin, bone, and mucous membranes attest the long silent period, frequently 20 years or more, before the development of the clinically recognizable malignant tumor (Burrows, 1928; Kruchen, 1937; Florentin, Jacob, and Hun, 1946; Glover, 1947; Cahan et al., 1948).

Exposure of the human ovary to sterilizing doses of x-rays results in atresia of the follicles. If the dose is small, a certain proportion of the primordial follicles may escape (Desjardins, 1932). Even after fairly intensive irradiation, the ovaries may retain their capacity for estrogen production although the ova have been destroyed (Miller, 1930). Kaplan (1939, 1945) reported the case of a young girl who had normal menses despite pelvic irradiation with 3,300 r. of x-ray and 990 mg. hr. of radium. Experimentally, Schmidt (1938) has found that irradiation of the ovaries of guinea pigs with a minimum sterilization dose of x-rays leads to the replacement of the normal ovarian structure by "interstitial gland" and cysts, accompanied by prolonged estrus with mammary gland development and urinary excretion of estrogen. Within a year, endometrial cysts were common; and in two years the uterine glands were irregular, distorted, and increased in number. The postmenopausal years in the human being are associated with an increased production of follicle-stimulating hormone. Essenberg (1947) has recently shown that the x-ray damaged ovaries of young mice respond to this substance with the production of active germinal epithelium and the formation of young follicles, although their ova soon atrophied. Even in the absence of extraneous hormonal stimulation, the mouse ovary, after recovery from its initial depression from exposure to x-rays, undergoes a phase of regeneration in which proliferation of the germinal epithelium and granulosa cells occurs to such a degree that granulosa-cell tumors often result (Furth and Butterworth, 1936; Traut and Butterworth, 1937; Geist, Gaines, and Pollack, 1939). The endocrine function of these tumors was indicated by the endometrial hyperplasia and the increased incidence of mammary tumors in the mice which bore them. Traut and Marchetti (1940) mentioned 2 cases in which granulosa-cell tumors were found in women who had had previous treatment with intrauterine radium, but they carefully avoided attaching any significance to this observation.

Even less than x-rays would a menopause-inducing dose of intrauterine radium be expected to cause a cessation of ovarian function. The cancericidal emanations from radium placed within the cavity of the uterus extend over little more than a radius of 3 cm. Effects of smaller doses on ovarian hormonal production are variable. Neumann and Péter (1932) demonstrated estrogenic hormone in the blood of several patients many months after the induction of a radium menopause with 2,500 mg. hr. of the element. It is possible that in some cases the amenorrhea which results from intrauterine radium depends primarily on its local sclerosing effect on the uterus.

There is considerable evidence to the effect that the estrogenic factor is important in the genesis of endometrial cancer (Taylor, 1944). In another

paper, additional evidence will be presented to support this view. Carcinoma of the endometrium is exceedingly rare following surgical castration. Radiotherapeutic "castration" lacks this prophylactic effect. The difference is probably ascribable in part to the continued production of estrogen by the ovaries of at least some patients who have been subjected to a radiation menopause.

Many gynecologists have the impression that the incidence of endometrial cancer is on the rise. This impression is substantiated by the records of the Roosevelt Hospital. The average annual number of cases of this disease treated in this clinic during 1945 and 1946 was approximately double that for the preceding eight years, although the clinic population has remained practically stationary. Several possible factors may be mentioned in explanation of this increase; namely, an increasing life span of the population, more frequent resort to curettage, and improved diagnosis. Two additional factors of possible significance are the common use of estrogens for menopausal symptoms during the past decade, and the treatment of benign pelvic conditions by irradiation, a method of treatment which has been in popular use in this country during the past 25 years. In 5 of the 21 cases in the present series the diagnosis of fundal cancer was made during the last two years.

A disproportionate number of sarcomas appear in the literature among the reported cases of malignant tumors of the uterine corpus which occurred following pelvic irradiation. Vogt (1926) reported 3 sarcomas to 3 carcinomas; Martindale (1933) recorded a sarcoma of the fundus and one of the cervix to 2 endometrial carcinomas; Scheffey (1942) had 1 sarcoma to 4 carcinomas; and Burnam (1942) observed 1 sarcoma to 5 carcinomas. In a study of 20 cases of sarcoma of the endometrium, McDonald, Broders, and Counseller (1940) noted that 2 of their patients had had the menopause induced previously by means of radium or x-rays. Novak and Anderson (1937) reported a case of polypoid cervical sarcoma in a 38-year-old woman in whom an x-ray menopause had been induced 8 years previously because of uterine bleeding.

The histologic classification of the 21 cases in this series likewise shows an unexpectedly high incidence of 6 sarcomas (29 per cent), whereas the incidence of sarcomas among all the malignant tumors of the fundus recorded in the clinic is only 6 per cent. Carcinosarcomas and malignant mixed tumors have been classified as sarcomas. Of the 4 patients with malignant mixed tumors of the fundus who have been treated in the Roosevelt Hospital, 3 had a history of treatment with intrauterine radium for benign conditions nine to fourteen years previously. The reader is referred to the paper by Liebow and Tennant (1941) for a description of this type of tumor and a review of its literature. Another finding of incidental interest was the 3 cases of adenoacanthoma, an uncommon but by no means rare type of endometrial neoplasm.

The significance of the high incidence of sarcomatous tumors among previously irradiated uteri is brought into clearer focus by a consideration of experiments begun in 1933 by Lacassagne in France. This worker found that sarcomas could be produced in the thighs of rabbits by a single exposure to 610 r. of high voltage x-ray following the induction of a local inflammatory lesion with either bacteria or sterile irritants. The average latent period for the

appearance of the tumors was 1½ years. Neither inflammation nor irradiation alone sufficed to produce the tumors; both were required. These experiments were repeated and the results confirmed by Burrows, Mayneord, and Roberts (1937) and by Burrows and Clarkson (1943). The latter authors stated that the possible danger of causing neoplasms in man by irradiating inflamed tissue has been overlooked because of the long interval between cause and effect. The human endometrium almost always shows evidence of a chronic inflammatory reaction after a period of prolonged bleeding. Irradiation of such uteri perhaps fulfills the requirements for the induction of sarcoma as established experimentally. Recent experiments by Figge (1947a, 1947b) have further interest for the problem. This author found that the intensified cosmic rays to which mice were exposed when their cages were covered with lead plates resulted in a decreased latent period for the appearance of subcutaneous sarcomas following the injection of methylcholanthrene. Radium has caused osteogenic sarcomas to develop in rats (Dunlap et al., 1948).

More recently carcinoma of the uterus has been produced in rabbits by exposing the animals to x-rays (Lorenz, Eschenbrenner, Heston, and Deringer, 1947).

The evidence presented in this paper falls short of proving that radiant energy is carcinogenic for the human uterus. Combined with the clinical and experimental data in the literature it is believed to be sufficiently suggestive, however, to warrant further study of the problem and to temper, in the meantime, the enthusiasm which many gynecologists have for pelvic irradiation in the treatment of benign conditions of the uterus. Figge (1947c) has formulated a concept of cocarcinogens, suggesting that cancer may be caused not by a single substance but by two, three, or more interdependent noncarcinogenic agents. It is possible that radiant energy may fall into this category. The following excerpt from a recent editorial in the *Journal of the American Medical Association* (Vol. 138, 214-215, Sept. 18, 1948) seems pertinent: "Roentgen treatment for benign conditions should be used only with a vivid appreciation of its capacity for harm and with an overt evaluation of its presumptive benefits weighed against the known and possible injuries inseparable from its use in effective dosage."

Summary

1. Twenty-one patients among 270 with malignant tumors of the body of the uterus (8 per cent) gave a history of previous irradiation of the pelvic organs with radium or x-rays for benign conditions. The incidence of previous pelvic irradiation among patients with cervical carcinoma, by contrast, was only 0.3 per cent.

2. Six of the 21 tumors contained sarcomatous elements. This was five times the incidence of sarcomas among all the malignant tumors of the uterine fundus.

3. The average time interval between irradiation and detection of the uterine cancers was 8.3 years.

4. These findings, together with previously published data in the literature, suggest a possible carcinogenic effect of radiant energy on the human uterine fundus.

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A TECHNIQUE TO AID IN THE DETECTION OF MALIGNANCY OF THE FEMALE GENITAL TRACT*

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NOTWITHSTANDING the expenditure of large amounts of energy and money, the cancer problem has not been solved. Unquestionably, a great deal has been learned about atypical growth, but significant clues to the origin of malignancy are few. Most of the studies seem to fall fairly readily into three groups. One of these has been the search for a causative agent, a virus, or some-other initiating factor. No less important has been the work of the chemists studying the metabolism of malignant cells, the enzyme systems involved, and the effects of various circulating chemicals in the blood, such as hormones. Finally, there has been a number of studies pointing to the importance of the constitutional or genetic factor.

There is, however, another aspect to the problem to which little attention has been given. Malignant cells not only seem to be different chemically from normal cells but, more particularly, they exhibit profound disturbances not so much in the character of individual cells as in the relationship which cells bear to each other. In normal growth and differentiation, changes occur not only in the internal pattern of each individual cell, but also in the way these cells are grouped and linked together to form characteristic tissues and organs. In malignancy, it is this necessary relationship between cells that is lost. The basic problem, therefore, is: What has happened to the forces which in normal growth define the pattern of organization of tissue and organs of the whole organism[2]? This, of course, is another way of saying that cancer is but a special case of the central problem of all biology, the origin of design of the living system; for it is the breakdown of the forces of organization which is at the heart of the problem.

Explanations of the origin of design have been offered by Aristotle, Descartes, Driesch, and Childes, to name but a few, but they have not been entirely satisfactory. As natural-history descriptions of biologic events, these have been interesting, unquestionably, but as sharply defined descriptions of the nature of the forces involved, they have been of little help.

A number of years ago, consideration of the problem of organization of the developing nervous system led to an attempt to solve this problem in a different manner.[1, 5, 13] Since it has long been known that electrical activity is a common

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attribute of living systems, it was suggested that such electrical manifestations were evidence of an electrodynamic field in all living beings, and that it was this field which, through its inherent forces, imposed design on living matter. Evidence supporting this hypothesis has been accumulated and has been summarized recently.[4, 13, 14]

If, then, cancer is a special case of the problem of organization, it should follow that atypical growth should be accompanied by significant alterations in the characteristic field properties of a living organism. That this is the case has been shown in studies of malignancy in mice.[3, 7, 8, 9] In all these studies, however, it was very disappointing to find that, while the changes in the field were statistically significant, they were useless so far as the individual organism was concerned. A number of factors probably explain this lack of individual significance. Biologic variation of both the host and the growth, the unfortunate necessity of tying the animal down for observations, and the relatively low potentials obscured the final results. However, the statistical evidence was sufficiently strong to warrant the extension of the procedure to the problem of cancer in human beings.

In the clinic, there are numerous diagnostic techniques with which electrometric records can be correlated. A careful study may, therefore, yield significant results in at least three cases. In the first of these there may be uncovered a significant electrometric correlate of malignancy. Secondly, there may appear a significant relationship between the electrometric findings and the rate of development of malignancy. Finally, since all these results derive from the field properties which define the design of the organism, it may be that an electrometric pattern will be found which can either indicate the existence of malignancy before the other standard methods of analysis or perhaps predict the constitutional type which may, at some later period, and under proper conditions, develop cancer.

Finally, if these studies should yield significant results, it would follow that cancer is a defect in the design of the organism which a wide variety of causative agents may be expected to uncover. There would be, therefore, no cause of cancer in the sense of an agent, but rather a constitutional or field defect which may develop into cancer as a result of any one of a wide number of external or internal factors.

To test the above hypothesis, an experiment was set up on the Gynecological Service of Bellevue Hospital. The technique employed follows in detail, in the hope that similar studies in other clinics will be carried out. The results of the first 428 cases are included as a preliminary report. The study is, at present, being continued with a grant from the National Cancer Institute of the United States Public Health Service and the clinical results will be published at some later date.

Technique

A number of primary assumptions underlie the application of direct current measurements to a cancer problem. The first of these is that the living system possesses as one of its attributes an electrodynamic field. A second is that

variations in biologic activity are correlated with variations in the electrical characteristics of the field. It is these variations in field properties that can be measured in part by means of determination of standing potential differences. However, such measurements, in order to be consistent and reproducible, ideally must be made as pure voltage gradients independent of current and resistance changes. For this purpose, the electrometer of the physicists should be the instrument of choice. Unfortunately, this is a difficult instrument to handle except under very rigorous conditions. To simplify the problem, therefore, a vacuum tube microvoltmeter was designed[6] with sufficiently high input impedance to reduce current and resistance in the system being measured, to a negligible value. The circuit developed is essentially a Wheatstone bridge, using two vacuum tubes or a twin tube, and fixed resistance as the third arm in the bridge, with the potential differences to be measured imposed across 10 megohms on the fourth arm of the bridge. Any voltage gradient across the 10 meghoms unbalances the bridge so that the resulting changes in plate current can be read on a suitable galvanometer. Again, the potential difference must be read by means of some contact with the living system which does not develop self-potentials and which are completely reversible. For this purpose, silver-silver chloride electrodes were chosen, operating in physiologic salt solution, which latter is brought into contact with the living organism through any convenient procedure. Finally, since this technique reports changes in potential differences in the inherent field, it is possible to make a great many determinations without disturbing the system measured.

The particular instrument used in this study consists of a twin triode, 2-C21, 1642, in a bridge circuit employing a cathode follower (Richter). The cathode follower resistance is variable and by means of the double pole, double throw input switch the control grid can be balanced at free grid potential. This is an absolutely necessary condition of operation. Power is supplied to the bridge through a standard power pack which, however, must be operated in conjunction with a voltage regulating transformer (Solar). The output from the plates is fed to a General Electric photo-electric recorder with a 3 microampere full scale deflection. The galvanometer in this instrument should have critical damping resistance of approximately 10,000 ohms. By interposing a 10,000 ohm potentiometer between the output of the bridge and the input to the galvanometer, the over-all sensitivity can be set at any desired multiple of one millivolt per unit deflections. Since virtually no current is drawn from the system measured, null point determinations are unnecessary and the recorder can be used as a straight deflection instrument. A complete circuit is shown in Fig. 1.

Calibration of the apparatus can be most easily performed using a Leeds and Northrop student type potentiometer. With this, it is possible to introduce into the microvoltmeter any desired number of millivolts. These will be recorded by the movements of the pen in the recorder. The connection of the electrodes to the instrument and of the instrument to the recorder should be so arranged that when the pen moves to the right of the zero point, the "hot" or control electrode will be positive to the reference electrode by the imposed number of millivolts. Conversely, movement of the pen to left of the zero point means that the control electrode is negative to the reference electrode by the imposed number of millivolts. Normally, it has not been found necessary to ground any part of the apparatus, but there are circumstances when a ground is necessary, especially where there is a good deal of other electrical apparatus in the environment. This is accomplished by running a lead from the reference electrode binding post to any suitable external ground. It may be advisable to shield the leads from the electrodes to the instrument. Finally, the table on which the

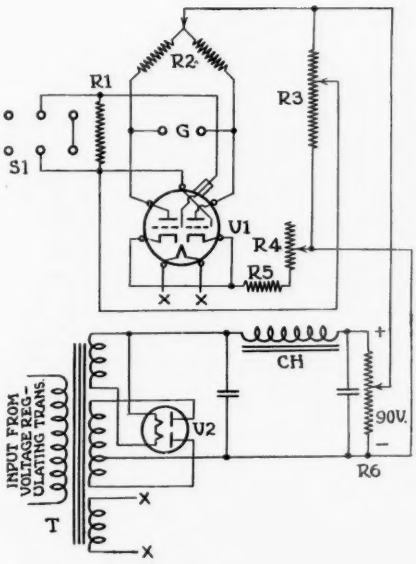

Fig. 1.

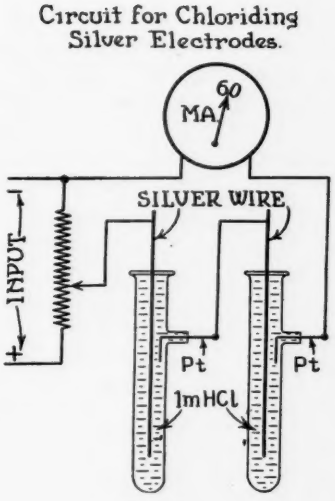

Fig. 2.

Fig. 1.—Microvoltmeter circuit. S1—General radio switch, type 339-B, R1—10 megohm resistor, S. S. White, R2—10 K helipot, R3—100 K 50W. Semivariable. Clarostat tap at 65 K ohms, R4—10 K General radion potentiometer type 301-A, R5—20 K fixed wire wound IRC, R6—Same as R3, T—Transformer UTC R-2, CH—Choke, G—Galvanometer in G.E. photoelectric recorder, V1—RCA Twin Triode 2C21/1642, V2—RCA rectifier type 80 or equivalent.

Fig. 2.—Circuit for chloriding electrodes.

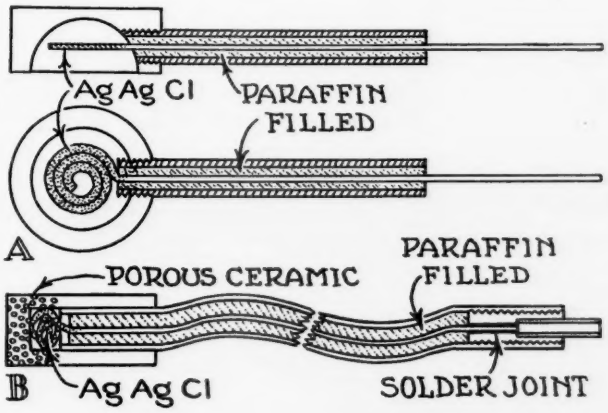

Fig. 3.—Diagram of plastic holders for electrodes. Connections of silver wire to leads to microvoltmeter must be protected from moisture.

patient lies should be insulated on glass cups and all parts of the instrument should be supported on insulating material. In rooms to which run alternating current lines, adequate grounding of the apparatus may be necessary.

The electrodes used are standard silver-silver chloride electrodes made by chloriding pure silver wire in molar hydrochloric acid at 40 milliamperes for five or ten minutes.* (Fig. 2.) The reference electrode which was placed on the ventral abdomen just above the symphysis pubis, is shown at *A* in Fig. 3. The holder can be readily constructed from a short segment of lucite rod. The center of this is drilled out to make a deep cup and a hole drilled through the side wall into which is cemented a short length of smaller diameter lucite tubing. A castolite casting may also be used. (Fig. 3.) The silver electrode may be inserted into this side arm with the active end of the electrode in the bottom of the well. The well can then be packed in cotton soaked in physiologic salt solution. This type of holder has certain advantages in that it can be made rapidly and the cotton plug can be replaced after each measurement. An air filter, such as is used to aerate aquaria and which, therefore, is porous, may be drilled out to make a chamber in which the exposed tip of the silver-silver chloride can be placed. A side arm of amphenol tubing to hold the electrode in position is cemented on. All but the flat face of the chamber is then given several coats of a waterproof plastic—in this instance, Phenoplast. This unit, when soaked in physiologic salt solution, provides adequate electrical contact with the skin. The vaginal electrode was constructed from a piece of lucite tubing, approximately one-half inch in diameter, formed into a shallow *S* curve after heating in boiling water, and the whole interior filled with paraffin after insertion of the silver wire. The active portion of the electrode projects a quarter of an inch beyond the lucite tube and may be covered, after chloriding, with cotton or gauze soaked in saline or, as in the final form, by a small section of filter tubing. This electrode is diagrammed at *B* in Fig. 3. Electrodes made in the above manner do not develop significant self-potentials over a considerable period of time. Usually it is wise to have a second pair available. If, however, a small potential difference, not to exceed 2 to 5 millivolts, appears between the electrodes when immersed in common salt solution, they can still be used. It is simply necessary, after immersing the two electrodes in common salt solution, to bring the recording pen to the arbitrarily selected zero in the center of the recording paper by means of the zero controls. (Fig. 1.) The reference electrode is then placed on the abdominal skin, with the patient in a recumbent position, and held there by any convenient bandage. The vaginal electrode may then be introduced, placing the protected tip in the posterior fornix of the vagina against the cervix. With the patient resting quietly and undisturbed by the electrode placement, a continuous record of the potential difference between the ventral abdominal wall and the cervix can be recorded for any convenient length of time, usually from fifteen minutes to one-half hour. At the start of such a record, there is often a drift to either negative or positive side of the zero point. This is not always present, but probably indicates that the whole electrode system is coming to equilibrium with the living organism. For the rest of the run, the potential difference will usually remain astonishingly constant with only minor variations. At the conclusion of the run, the two electrodes should be removed and placed in a common bath of salt solution. Any change in the zero point should be noted. This, however, rarely occurs if the technique is correct.

Finally, a word of caution. This is a highly specialized technique. The instruments are exceedingly sensitive and must be handled with care and with

*More recently, Dr. Theodore Shedlovsky prepared for this study a pair of electrodes made by fusing chemically pure silver chloride directly to the silver wire. These have proved eminently satisfactory.

understanding. There are many pitfalls which can be avoided only by practice and patience. The procedure, however, once mastered, becomes relatively simple, although never foolproof. Reproducible results come only after experience.

Discussion

The results of the study utilizing the technique described above are still far from complete, but a brief summary of four hundred and twenty-eight cases is presented as a validation of the procedure.

These cases fall into two clinical groups. Seventy-five patients belong in the group diagnosed clinically, and by pathological examination, as having malignancy in various stages of development; involving the cervix in sixty-one cases, the fundus in seven, the ovaries in six, and one patient in whom the malignancy was thought to be primary in the bladder.

Three hundred fifty-three patients fall into two groups, one with a wide variety of nonmalignant pathology, and one with no demonstrable pathology. Electrometrically, all but one of the first group showed a very evident electronegativity of the cervix with respect to the ventral abdominal wall. Only one case diagnosed as malignant gave a positive record. The magnitude of the negativity varied from patient to patient. There was no clear-cut correlation between this magnitude and the stage of malignancy. In at least one instance, although the electrometric record was negative, the pathologic report was equivocal. On a second biopsy, however, material was obtained from which a positive diagnosis of malignancy was obtained.

In the group of nonmalignant pathology, three hundred fifty-three in number, two hundred eighty-nine, in contrast to the first group, showed a significant and marked positivity of the cervix with respect to the ventral abdominal wall. As in the first group, the magnitude of the positivity varied from patient to patient and failed to show any significant relationship to the kind of pathology. The remainder of this second group, sixty-four, showed an electrometric negativity identical with that found in the cancer group.

The reasons for this finding are not entirely clear. There are, however, a number of possibilities. In the first place, eleven of these negative cases were fibroids. They are generally believed to be nonmalignant growths, but they are also atypical arrangements of uterine cells, hence the field changes may not be unlike those found in malignancy. Six of the patients in this group were intrauterine pregnancies. These are included to indicate that there are other factors than cancer which may be accompanied by field changes. A third group of eight cases are included because they represent another source of negativity of the genital tract, namely, ovulation. All of these patients were within the ovulatory time and exhibited no obvious pathology. The correlation of negativity with ovulation has been referred to previously.[11] Seven patients were postmenopausal and, as will be shown in a later report, a much greater incidence of negativity and malignancy is observed in the older age groups. The remainder of the patients in this group showing negativity of the cervix covered a wide range of pathology, including five ovarian cysts, four abortions, six cases of pelvic inflammatory disease, four cervical polyps, two granulomas of the cervix, etc.

Finally, however, the fundamental assumption on which this study is based suggests that the negativity in many of these patients may have predictive value. It is not at all impossible that these patients, although they have not yet shown clinical signs of malignancy, may possess the field defect which will, at some later date, and under the proper conditions, result in cancer. This possibility is so important that an adequate follow-up study should be made on these patients. They should be examined electrometrically at fairly frequent intervals for as long a period as possible, but not for less than five years.

This brief summary of the results on four hundred twenty-eight cases confirms the basic hypothesis that cancer is fundamentally the result of a failure of the organizational field forces in the living system. When measures of these field forces are properly made, obvious differences in the field properties of patients, with or without malignancy, have been determined. In three hundred fifty-three nonmalignant cases, two hundred eighty-nine showed the cervix to be positive with respect to the abdomen. A polar reversal of the field forces between the cervix and the ventral abdominal wall has been found in malignancy. This polar reversal is also found in 18.1 per cent of the nonmalignant pathology and in normal individuals.[10, 11]

It is to be noted that this study results from a deductively formulated theory of biologic organization derived from the postulational concepts of modern field physics. This theory was required by the inadequacy of chemical and thermodynamic concepts to explain the persistence of the necessary relatedness between the constantly changing entities of biologic systems.[15] In cancer, the primary defect is a breakdown in the normal controls of this necessary relatedness. Field forces are adequate in magnitude and direction for these controls. Hence, measurable alterations in the fields, showing departure from the paradic, correlate with malignancy, which is the result of the breakdown of controls of the pattern of organization in the living system.

Summary

1. A technique is described for measuring field forces in the intact human being.

2. In seventy-five patients with cancer of the female genital tract, seventy-four showed the cervix to be consistently electronegative to the ventral abdominal wall, 98.7 per cent.

3. Three hundred fifty-three patients with nonmalignant pathology showed the cervix to be electropositive to the ventral abdominal wall in two hundred eighty-nine instances, or 81.9 per cent.

4. In two hundred ninety patients showing the cervix to be electropositive to the ventral abdominal wall, two hundred eighty-nine, or 99.6 per cent were in nonmalignant conditions.

5. Sixty-four patitents, or 18.1 per cent of those with nonmalignant conditions, showed an electronegativity of the cervix similar to that found in cancer.

6. It is suggested that an unknown number of this latter small group may represent patients with field defects who may, at some later date, develop cancer.

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PREGNANCY AND HODGKIN'S DISEASE

With a Report of Three Cases

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THE basis for a rational approach to the management of pregnancy complicated by Hodgkin's lymphogranulomatosis is conceived with great difficulty. Careful search of the literature has revealed only 29 cases of Hodgkin's disease occurring during pregnancy (Table I) which are reported in detail and corroborated by adequate histologic study. The English and American literature has but five reports dealing with this problem, all but Adair[8] presenting single cases. Only Gemmell[2] does more than present a case history.

Three patients with Hodgkin's disease complicating pregnancy have been seen in the Tumor Clinic of the Boston Dispensary in the past ten years, of a total of twelve women with Hodgkin's disease admitted during this period. Each diagnosis was confirmed by histologic study, and this report presents the case histories of each patient. An analysis of the earlier reports together with these three cases is considered to be of some value in developing a basis for the management of the obstetric factors in this complex situation. The scarcity of this complication in obstetrics is attested to by the report of Palacios Costa, Chavanne, and Zebel Fernández[14] who found five cases of Hodgkin's disease in 30,000 gestations, or an incidence of 1 in 6,000 pregnancies.

Case Reports

CASE 1.—B.D. *No. 394442,* MRS. B. F., para 0, gravida i, abortions 1 (1-0-0-1-0), aged 29 years, was admitted to the Tumor Clinic of the Boston Dispensary on Sept. 22, 1939, with engorgement of neck veins and a roentgenographic picture of mediastinal masses suggestive of Hodgkin's disease. She reported a spontaneous abortion two months preceding her first appearance in the Tumor Clinic. She received 1600 r of external radiation with the 200 k.v. machine to the anterior and posterior chest over the next three months, and her symptoms and signs subsided. A bean-sized node in the left clavicular area was excised and microscopic examination revealed: fibrosis obliterating normal lymph node architecture, marked infiltration with eosinophiles, hyperplasia of the reticulo-endothelial cells, occasional characteristic Reed-Sternberg cells, edema, cellular infiltration of the capsule extending out into the periglandular tissue, and areas of necrosis. A diagnosis of Hodgkin's disease was made. She received an additional 2700 r to the anterior and posterior chest and left supraclavicular areas over the succeeding three months. Her general condition was improved. On April 11, 1940, a diagnosis of intrauterine gestation of fifteen weeks' duration was made, her expected date of confinement being October 25, 1940. The mediastinal shadow continued to enlarge in spite of the roentgen therapy. Obstetric consultation at that time expressed reluctance to advise interruption of the gestation. In the next three months a total of 4500 r were administered to the chest. There developed increasing dyspnea, choking spells, and edema of the neck and clavicular skin area in the last trimester, and 5000 r of therapy was administered to the

mediastinal area during this time. Extensive infiltration of both lungs was found in her eighth month of gestation. Almost constant therapy kept this patient moderately comfortable, although a chronic cough and increasing dyspnea persisted. In all, a total of 11,000 r of roentgen therapy had been administered in a period of eight months. Additional tumor masses developed in the mandibular and clavicular areas. Her condition showed progressive deterioration, and she was admitted to the hospital on Aug. 9, 1940, for acute gastroenteritis and again at thirty-four to thirty-six weeks' gestation because of rapid deterioration of her physical state. Labor was started by artificial rupture of membranes, and she delivered by low forceps under local anaesthesia a 2150 Gm. male infant in good condition, who survived for four days. The first few days post partum the course was uneventful and afebrile, but on the eighth day of the puerperium the patient began to go downhill rapidly and expired that evening. Postmortem examination of the baby showed massive atelectasis, and no evidence of damage from the roentgen therapy which had been administered during her pregnancy. The placenta was examined and found to be entirely normal. A postmortem on the mother was not obtained.

CASE 2.—B.D. *No. 4137*, Mrs. E. G., aged 20 years, was first seen in the Tumor Clinic of the Boston Dispensary on Dec. 23, 1941, for a bulge in the left supraclavicular fossa. Biopsy of these glands revealed the typical findings of Hodgkin's lymphogranuloma in the stage of almost complete sclerosis. She received 200 k.v. machine roentgen therapy to this area (600 r) and later to the skull for severe headaches which were considered to be on the basis of the Hodgkin's disease. She remained in a state of remission for three years when she again received 450 r at 200 k.v. to the neck for recurrent glandular involvement. She was followed in the Memorial Hospital, New York City, for one year where she received additional roentgen therapy (2,700 r) and was returned to the Boston Dispensary for further care on May 17, 1946. On November 15, 1946, she received deep x-ray therapy, 200 k.v., in two doses delivered to the left axilla, a total of 1,000 r. In January, 1947, roentgen evidence of mediastinal involvement was found. Additional therapy (2,700 r) was given to the mediastinal area in February, 1947. This was followed in April, 1947, with 1,100 r to the lumbosacral and left axillary regions. She remained quiescent in her remission and became pregnant for the first time in April, 1947. In view of the deep x-ray therapy over the lumbosacral area unwittingly administered at the same time that conception occurred, it was felt that continuation of the gestation was not advisable. A dilatation and curettage were therefore performed and a fetus of approximately eighty-five days of age was obtained. The endometrium was normal for pregnancy, the placental tissue normal, and there was little evidence of injury to the fetus. This patient has remained well up until the time of publication of this paper, six years after the onset of Hodgkin's disease, and is now six months post partum.

CASE 3.—B.D. *No. 5093*, Mrs. C. DeP., aged 23 years, was first seen in the Tumor Clinic of the Boston Dispensary on April 27, 1945, with a complaint of recent swelling of the glands in the neck. A biopsy revealed a patchy but striking eosinophilia, especially about the capsule, some monocytic infiltration in the same areas, occasional Reed-Sternberg cells, and areas of cellular deterioration and cytophagocytosis in the center of the nodule. In spite of some disagreement among pathologists, it was decided that this was Hodgkin's paragranuloma. Roentgen treatment to the involved areas was undertaken, and she received 1,200 r with the 200 k.v. machine in May, 1945. Her course was uneventful and the glands subsided after radiation. Because of recurrent enlargement of the nodes of the neck, she was offered 1,200 r again seven months later. Following an asymptomatic period of five months, 600 r were again applied to the neck. In August, 1946, she was found to have a two months' normal gestation. There were no unusual changes in her physical status, and the pregnancy proceeded normally until Feb. 25, 1947, at thirty-six weeks in her pregnancy, when she was admitted to the hospital for pelvic cramps and vaginal bleeding. A roentgen diagnosis of low placental implantation (? previa) was made. She was discharged after one week and returned to the hospital one month later with moderately severe vaginal bleeding and the absence of fetal heart tones. She went into labor and delivered naturally an apparently normal stillborn

macerated baby with a true knot in the cord. The patient sustained some cervical and vaginal lacerations during parturition for which she was treated with transfusion and streptomycin. She was discharged in good condition but re-entered April 23, 1947, one month post partum, for vaginal bleeding. A dilatation and curettage were performed and placental site bleeding remedied. Examination at that time revealed a small right cervical node and her liver was palpated 1 cm. below the costal margin in the midclavicular line on deep inspiration. She was asymptomatic in remission at the time of this report.

Discussion and Analysis

The clinical and pathologic changes of Hodgkin's lymphogranulomatosis are too well known and widely studied to require comment here. Our concern is entirely with the obstetric aspects of the problem.

Reference to the standard contemporary source books for opinion concerning the management of pregnancy complicated by Hodgkin's disease is of little avail. Stander,[16] De Lee and Greenhill,[17] Davis,[18] Titus,[19] Adair and Stieglitz,[20] and Halban and Seitz[21] do not mention this problem at all. Adair[8] states that "the effect of Hodgkin's disease combined with pregnancy is not known, but, judging from the two cases who have been registered at the Chicago Lying-in Hospital, the prognosis seems to be unfavorable. Neither of these patients became markedly worse during pregnancy. . . . The possible accelerating effect of pregnancy on the condition and the generally fatal outcome, then, are the reasons for considering pregnancy undesirable in Hodgkin's disease patients." At the present time not a single modern expression of opinion based on more than two cases has been found which would be of value to English readers. Berkeley and Bonney[22] in 1913 stated that "Hodgkin's disease may first declare itself during pregnancy, or pregnancy supervening upon it, the course of the disease may be much accelerated." They felt that abortion is very common and that the anemia concomitant with the process may lead to retroplacental and postpartum hemorrhage. In their opinion pregnancy should be terminated. Since there has been no recent analysis of pregnancy complicated by Hodgkin's disease, it was felt that studies of all the cases available might clarify some of the many ramifications of the problem.

Gemmell[2] studied 57 cases of Hodgkin's disease in women and found that about one-half occurred during the childbearing period. Approximately 16 of these were married, and six of these married women dated the onset of their disease from some pregnancy. In addition, in the 17 women in whom a menstrual history was available, 14 had some degree of oligomenorrhea. Thus, in nearly one-half of the women in his series, the onset of Hodgkin's disease occurred during a period of physiologic amenorrhea. The labors in the six cases available for his study were normal in five instances and presented a postpartum hemorrhage in one case. The puerperium was normal in five cases and febrile in one which expired on the one hundred ninetieth day post partum. Three spontaneous abortions occurred which were not considered related to the Hodgkin's disease. One premature labor (seven months) occurred and was also felt to be incidental. He felt that estrogens played an ameliorating role in the process.

Study of Table I reveals that there are twenty-four parturients in the literature whose age can be established during pregnancy complicated by Hodgkin's disease. The average age of these women is 28.3 years, with 15 falling in the 20- to 29-year-old group, and nine in the 30- to 39-year-old group. The youngest patient reported was 20 years old, and the oldest 39 years of age. Herz[4] states that the disease is most frequent during the 30- to 50-year-old age period. Epstein[23] reported Hodgkin's disease one-third as frequently in women as in men, and felt the process to be less malignant in women. In 204 cases he found

the average survival period to be 3.4 years in women and 2.3 years in men. He stated that 92 per cent of women with Hodgkin's disease between the ages of 30 to 50 years survive three or more years.

It is of possible significance that Hodgkin's disease has not yet been reported in pregnancy before the age of 20 years nor beyond 39 years of age, although the disease itself tends to show a progressive rise in incidence up to 60 years of age.[24] The incidence of pregnancy is greatest between 20 and 30 years of age, and this fact would account for the fifteen cases reported in this age period out of a total of twenty-four cases in which age is stated. There is apparently no significance in the relations of the age of the patient, Hodgkin's disease, and pregnancy.

Information sufficient to establish the number of pregnancies is available in twenty-three of the twenty-nine cases reported. Analysis of the number of pregnancies in the reported patients reveals that 44 per cent (ten) were primigravida, 35 per cent (eight) were gravida ii, and 4 per cent (one) were gravida iii, 9 per cent gravida iv, and 9 per cent gravida v. There are thus 10 primi- and 13 multigravidous women in whom parity is reported. The incidence of the Hodgkin's disease in the 13 women who have had more than one gestation out of a total of 23 does not appear to lend weight to the theory of Gemmell that ovarian hyperactivity as indicated by the increased ovarian activtiy in pregnancy acts as a strong deterrent to Hodgkin's disease.

Consideration of the onset of Hodgkin's disease with relation to pregnancy reveals that sixteen of the twenty-nine cases in which adequate information is available reported the discovery of Hodgkin's disease after the diagnosis of pregnancy had been made. It is, of course, likely that the process antedated gestation in some if not all of these thirteen cases. This fact appears to be in accordance with the findings of Desjardin[25] who reported that estrogens had little or no effect on the course of Hodgkin's disease, especially in the light of the 55 per cent of the total number reported who dated their onset during gestation.

The pregnancies were permitted to terminate spontaneously in thirty-two gestations of a total of forty-two pregnancies in twenty-nine patients. In only seven reported patients, including one personal case, was the pregnancy interrupted before viability of the fetus because of the presence of Hodgkin's disease. Only Blitz (two cases) and Perrier (two cases) carried out this procedure in more than one instance. In none of these cases did the therapeutic abortion result in exacerbation of the Hodgkin's process. In our own case the patient has remained in a state of remission since her abortion six months ago.

Two women had three pregnancies, four had two pregnancies after the diagnosis of Hodgkin's disease had been made. The largest number, twenty-eight of thirty, cases at term, had a normal spontaneous delivery. There were but three spontaneous abortions apparently unrelated to the process. One patient had labor induced medically in the last trimester and one was delivered by cesarean section because of massive edema of the vulvar tissues. There is little evidence that spontaneous abortion occurs with significantly increased frequency in Hodgkin's disease. There is as well no evidence that acute intra- or postpartum hemorrhage occurs with increased incidence during Hodgkin's disease. In fact, uterine bleeding is rare in Hodgkin's disease. The labors are apparently normal in onset, duration, course, and termination, except in the one case that came to cesarean section because of excessive vulvar edema which may have been related to the lymphogranulomatosis. The puerperium was apparently normal in all instances from an obstetric standpoint. In no case was toxemia of pregnancy reported.

In three cases the fetus was involved in the maternal Hodgkin's disease at birth. A rather heated controversy has been aired in the German literature concerning the transmission of Hodgkin's disease across the placenta to the fetus.

TABLE I. REVIEW OF LITERATURE ON

NO.	YEAR	NO. OF CASES	AUTHOR	AGE AT ONSET	GRAVIDITY AT ONSET	DURATION OF PREGNANCY AND/OR HODGKIN'S DISEASE	INTERRUPTION OF GESTATION
1.	1911	1	Davis, A. B.[1]	32	v	Hodgkin's disease onset at 6 months' gestation	No
2.	1923	1	Gemmell, A. A.[2]	23	ii	Hodgkin's disease onset at 4½ months' gestation	No
						1½ years later	No
						2 years later	No
3.	1926	1	Priesel, A., and Winkelbauer, A.[3]	31	iii	Hodgkin's disease onset in first trimester	No
4.	1934	5	Herz, A.[4]	?	?	Hodgkin's disease onset early post partum	No
				?	?	Hodgkin's disease onset "shortly" after parturition	No
				?	?	Hodgkin's disease onset "before" parturition	No
				?	?	Hodgkin's disease onset "long before" gestation	No
				?	?	Hodgkin's disease onset at 9 years of age	No
5.	1934	1	Luetkens[5]	?	?	?	No
6.	1938	1	von Braitenberg, H.[6]	29	?	Hodgkin's disease onset 1 month post partum	No
7.	1939	1	Horster, H.[7]	22	i	Pregnancy in 4th year of Hodgkin's disease	No
						2nd pregnancy in 6th year of Hodgkin's disease	Yes
8.	1940	2	Adair, F. L.[8]	24	ii	Hodgkin's disease onset 3 years before gestation	No
						2 years after abortion above	No
						2 years after delivery above	Yes
				22	i	Hodgkin's disease onset 7 years before gestation	No
9.	1940	1	Parade, G. W.[9]	22	i	Hodgkin's disease onset 2 years before gestation	No
10.	1940	2	Blitz[10]	?	?	Hodgkin's disease onset "before" gestation	Yes
				?	?	Hodgkin's disease onset "before" gestation	Yes
11.	1941	1	Kushner, J. I.[11]	27	ii	Hodgkin's disease onset 16 months before gestation	No
12.	1942	1	Parade, G. W.[12]	31	iv	Hodgkin's disease onset in 1st trimester of gestation	No
13.	1942	1	Klawans, A. H.[13]	33	i	Hodgkin's disease onset at 24 weeks of gestation	No
14.	1945	5	Palacios Costa, N., Chavanne, F. C., and Zebel Fernández, O.[14]	22	iv	Hodgkin's disease onset at 6th month of gestation	No
				29	i	Hodgkin's disease onset "before" gestation	No
				27	i	Hodgkin's disease onset at 4th month of gestation	No
				30	v	Hodgkin's disease onset at 5th month of gestation	No
				23	i	Hodgkin's disease onset at 4th month of gestation	No

HODGKIN'S DISEASE DURING PREGNANCY

MODE OF DELIVERY	COURSE AND OUTCOME OF HODGKIN'S DISEASE	RECOMMENDATION
Natural at term	Severe exacerbation during pregnancy. Died 119 days post partum	None
Natural at term	No effect on Hodgkin's disease	
Post-influenzal abortion 3½ months	No effect on Hodgkin's disease	Interruption advised when Hodgkin's disease found in early gestation. No interference advocated late in pregnancy
Natural at term	No effect on Hodgkin's disease	
Natural at term	Exacerbation post partum, death "shortly" afterwards. Postmortem reported	None
? Natural at term	Exacerbation post partum for 4 months, then remission	
? Natural at term	Exacerbation post partum for 6 months, then remission	Interruption early in gestation advised
? Natural at term	Exacerbation post partum, then remission for 1 year	
? Natural at term	Exacerbation post partum	
? Natural at term	Exacerbation intrapartum following remission of many years	
? Natural at term	Exacerbation post partum, died in 3 months. Child developed Hodgkin's disease at 33 months	Interruption early in gestation advised
Natural at term	Exacerbation post partum, died "shortly" after. Postmortem reported	None
Natural at term	Exacerbation post partum	Interruption early in gestation advised
Vaginal hysterotomy at 4 months	No exacerbation following abortion	
Spontaneous abortion 1st trimester	No effect	
Natural at term	No effect	Interruption of gestation suggested
Abdominal hysterotomy, 26 weeks	No effect	
Natural at term	No effect	
Natural at term	Exacerbation post partum, died in 4 months	Interruption of gestation not advised
Abortion at 3 months	Exacerbation early in gestation	Interruption of gestation advised
Abortion, 1st trimester	Exacerbation early in gestation	
Natural at term	No effect. Died 2 years post partum. Postmortem examination reported	Interruption of gestation not advised
Natural at term	Exacerbation post partum, died in 9 days. Postmortem examination reported	See above
Cesarean section at term for edema of vulva	No effect	Interruption of gestation not advised
Natural at term	Exacerbation post partum, died in 15 days	
Natural at term	No effect	
Natural at term	Exacerbation post partum	Interruption of gestation not advised
Natural at term	No effect	
Natural (?) at term	No effect	

TABLE

NO.	YEAR	NO. OF CASES	AUTHOR	AGE AT ONSET	GRAVIDITY AT ONSET	DURATION OF PREGNANCY AND/OR HODGKIN'S DISEASE	INTERRUPTION OF GESTATION
15.	1945	5	Perrier, H.[15]	31	ii	Hodgkin's disease onset 8 years before gestation	No
				37	i	Hodgkin's disease onset 8 months before gestation	No
				39	ii	Hodgkin's disease onset 4 years before gestation	No
						4½ years after gestation above	Yes
				29	ii	Hodgkin's disease onset 1 year before gestation	Yes
						1½ years after gestation above	No
				38	ii	Hodgkin's disease onset 2 years before gestation	No
16.	1948	3	Kasdon, S. C.	29	i	Hodgkin's disease onset 1 month before gestation	No
						6 months after above	Yes
				26	i	Hodgkin's disease onset 5½ years before gestation	Yes
				24	ii	Hodgkin's disease onset 14 months before gestation	No

Priesel and Winkelbauer reported the occurrence of Hodgkin's disease in a 4½-month-old child, histologically verified, in whom the mother had a histologic diagnosis of Hodgkin's disease as well. Although the midwife in retrospect many months later reported many nodelike elevations in the placenta, no study of the placenta was made. A second child is reported by von Braitenberg with signs of Hodgkin's disease first appearing at one month of age. He suggested the possibility of transmission of the disease from mother to child across the placenta. However, there is no clear evidence that Hodgkin's disease was present in the mother and no pathologic changes were noted in the placenta. Leutkens reported a case of Hodgkin's disease in a child 33 months old, whose mother died of this process at two months post partum. Nevertheless, all thirty remaining viable children (91 per cent) born of mothers with Hodgkin's disease have not been reported to have developed it later on. It is of interest that a possible case of accidental laboratory transmission of Hodgkin's disease has been reported by Horder.[33]

A normal child of 12 years is the oldest reported in the literature[26] born of a mother with Hodgkin's disease. In no case was there any evidence of placental involvement in the process. In no instance, as well, was there any evidence of damage to the fetus because of the use of roentgen radiation in the course of pregnancy. Adequate shielding of the fetus was used, of course, in all instances where roentgen rays were employed.

Analysis of the literature from the standpoint of the effect of the gestation and parturition on the disease is of special interest. In all, 40 pregnancies in 29 patients are available for study. Of these, 18 cases showed definite exacerbation of the Hodgkin's disease process during or immediately following the pregnancy. Thirteen of these occurred post partum and five ante partum. In 22 cases (55 per cent) neither pregnancy nor delivery resulted in an exacerbation. In view of the relatively short expectancy of life reported for women with Hodgkin's disease, this essentially equal incidence of exacerbations and remissions in the disease might be considered to be entirely due to chance. In any

I—CONT'D

MODE OF DELIVERY	COURSE AND OUTCOME OF HODGKIN'S DISEASE	RECOMMENDATION
Natural at term	No effect	
Natural at term	Exacerbation post partum	
Natural at term	No effect	
Interruption, 1st trimester	No effect, died 3 years post partum	Interruption of pregnancy not advised
Interruption, 1st trimester	No effect	
Natural at term	No effect. Exacerbation 3 months post partum, died at 6 months	
Natural at term	No effect on course. Died 5 years post partum	
Spontaneous abortion	No effect	
Induction of labor 34-36 weeks of gestation	Rapid progression of Hodgkin's disease through gestation with death 8 days' post partum	See summary and conclusions of this report
Abortion at 3 months	No effect	
Spontaneous at term	No effect	

case, the evidence from this standpoint is certainly not strong that Hodgkin's disease is activated by pregnancy. It would, of course, be of great value to know the incidence and frequency of exacerbations in a nine-month period in a comparable group of nonpregnant patients in order to state more clearly whether exacerbations in Hodgkin's disease occur with greater frequency during pregnancy. Craver[27] states he would expect a 50 per cent incidence of exacerbations in a nine-month period in non-pregnant Hodgkin's patients of this type.

TABLE II. DURATION OF LIFE POST PARTUM IN HODGKIN'S DISEASE FOR PATIENTS IN WHOM DEATH IS REPORTED IN THE LITERATURE

AUTHOR	YEAR	WEEKS
1. Davis[1]	1911	17
2. Priesel and Winkelbauer[3]	1926	"shortly after delivery"
3. Luetkens[5]	1934	22
4. von Braitenberg[6]	1938	"shortly after delivery"
5. Parade[9]	1940	29
6. Parade[12]	1942	1
7. Palacios Costa, Chavanne and Zebel Fernández[14]	1945	2
8. Perrier[15]	1945	156
9. Perrier[15]	1945	26
10. Perrier[15]	1945	364
11. Kasdon	1948	1

Table II presents the time after delivery in which death occurred in the eleven cases in which this evidence is available. The longest period of survival after delivery in which death is reported is seven years, and the shortest period is eight days. In no case did death occur before evacuation of the uterus. This would appear to be of great significance since one would ordinarily expect some of the twenty-nine patients to terminate their course fatally, but this has not yet been reported during the antenatal period in Hodgkin's disease. This evidence

would tend to lend some weight to the theory that the ovarian hyperactivity present in gestation acts as an inhibitor of Hodgkin's disease, and must be considered in the light of the evidence to the contrary presented earlier in this paper. It must be noted that in two cases of the seven where pregnancy was terminated by interference before viability of the fetus, it is possible to establish the survival period following the interruption of the pregnancy. It is impossible to draw definite conclusions from this meager material concerning the value of interruption of pregnancy for extending the survival time for women with Hodgkin's disease. It appears most likely that maternal survival is not significantly altered by early interruption of the gestation.

Consideration of the effect of early previable interruption of pregnancy upon the course of Hodgkin's disease is of major interest. Blitz reported two patients in whom interruption of the pregnancy was effected because of an exacerbation of the Hodgkin's disease in the first trimester of pregnancy. In both rapid remissions in the process obtained followed interference. Perrier reported the earliest exacerbation three months following previable interruption of the pregnancy. In no case did an acute exacerbation of the lymphogranulomatosis occur directly following induced abortion. This can be compared with the postpartum exacerbations occurring in thirteen of thirty-two cases (41 per cent) which went to term and were delivered. It appears likely from this consideration that exacerbations in the course of Hodgkin's disease are much more prone to follow delivery at term than delivery previably.

Only the case reports of Davis, Kushner, von Braitenberg, and Parade present postmortem examinations in the parturients. In none of these patients was there reported involvement of the ovaries or uterus in lymphogranulomatosis.

The recommendations offered in the management of pregnancy during Hodgkin's disease are available from eleven of the fifteen authors who have presented cases. Opinions are equally divided with six advising interruption of the pregnancy and five against interference in the course of gestation. It must be realized that in all cases these expressions of opinion are attitudes which are impossible to establish on a firm footing. Gemmell stated that the diagnosis of Hodgkin's disease early in pregnancy is indication for interruption. On the other hand, he felt that the reaction to early interruption of pregnancy would likely be as bad in advanced Hodgkin's disease as that at term. This is not substantiated by our analysis. He quotes several other British authors, such as Murray[28] in Albutt and Rolleston's *System of Medicine* that "parturition has . . . an unfavorable influence upon the progress of the disease." Gowers[29] is also quoted from Reynold's *System of Medicine* that "in one case only (of 25 fatal female cases) did the disease apparently commence during pregnancy. The progress of the disease was, in another, distinctly checked during pregnancy and it advanced rapidly after delivery." Dyes[30] felt that the response to x-ray therapy should determine the indication for interruption and that conservation of the fetus is advisable whenever possible. Parade felt that although the process may be aggravated by pregnancy, interruption should, nevertheless, not be advised routinely. The desire of the parents for the child plays an important part in the management of the pregnancy in his opinion, as in that of Herz. However, such humanistic considerations, intensely significant as they may be in practice, should play little part in the factual consideration of the intereffects of Hodgkin's disease and pregnancy. Perrier states that "there do not exist, in general, medical indications to interrupt a pregnancy in the course of lymphogranulomatosis." Gilbert[31] offered five cases of pregnancy out of thirty women reported with lymphogranulomatosis. Insufficient material is presented in all cases, however, for analysis. He states that remissions are uncomplicated after x-ray therapy for Hodgkin's disease during pregnancy. He feels that both marriage and pregnancy are to be discouraged in the presence of Hodgkin's

disease. However, if pregnancy occurs during a remission of the disease, he does not advise interruption of the gestation. A "wait and see" attitude best expresses his position.

Summary

A review and analysis of the available published literature on Hodgkin's disease and pregnancy with a report of three cases are presented. The need for such a study is clearly indicated by the complete absence of comprehensive information in the modern literature.

It is obvious from the reports of the multiple gestations during Hodgkin's disease that fertility is not grossly affected by the process. Spontaneous abortion, contrary to earlier statements, is also apparently unrelated to the presence of Hodgkin's disease in the light of but three occurrences in forty gestations. Hemorrhages occurring ante, intra, or post partum show no increased incidence in Hodgkin's disease. In spite of evidence to the contrary, there is considerable doubt that estrogens play a significant part in either the onset or severity of Hodgkin's disease.

Study of the age incidence reveals little of significance. The youngest patient was 20 years and the oldest 39 years of age, with an average of 28.3 years. There are 10 primi- and 16 multigravidous women. In sixteen of the twenty-nine cases in which sufficient information can be obtained, pregnancy occurred after the onset of lymphogranulomatosis. It is probable that the disease was present in some, if not in all, of the remaining cases before gestation developed. There does not appear to be any interference with ovulation or fertility by Hodgkin's disease from this fact alone, in contrast to the aberrations in ovarian activity which have been reported in leucemia.[32]

In all, thirty-two of a total of forty-two gestations were delivered at term. There were seven interruptions of pregnancy before viability of the fetus, and three spontaneous abortions which were not considered to be related to the lymphogranulomatosis. The largest number, twenty-eight of thirty, delivered naturally and spontaneously at term. One patient was induced medically, and one patient was delivered by cesarean section because of excessive vulvar edema. The latter indication for hysterotomy may have been related to the presence of Hodgkin's disease, but is an exceedingly rare complication in a rare complication of pregnancy. The problem of placental transmission of Hodgkin's disease to the fetus should be considered as a possibility. Of the three reported instances of Hodgkin's disease in young infants, the diagnosis of Hodgkin's disease is unquestioned in two of the mothers. On the other hand, all other viable children born of mothers with Hodgkin's disease have been found to be free of the disease. It can be stated that Hodgkin's disease is transmitted from the mother to the fetus across the placenta in 9 per cent of reported cases. Lymphogranulomatosis has not been reported in the placenta or membranes.

Adequate shielding has prevented the occurrence of radiation injury to the fetus in all cases where roentgen therapy was employed in exacerbations of Hodgkin's disease. Thus far there have been no reports of pregnancy in Hodgkin's disease treated with nitrogen mustards. Evaluation of this new therapeutic tool in the management of lymphogranulomatosis must await further study.

Of greatest significance is the evidence which can be applied to the establishment of an attitude which will determine the management of pregnancy in Hodgkin's disease. In view of the fact that exacerbations in the process occurred in but eighteen of forty-two gestations during Hodgkin's disease, it is felt that this is little more than the incidence of exacerbations in Hodgkin's disease which one would expect without pregnancy in a comparable group of women. Of the eighteen patients who developed exacerbations during the gestational and puerperal period, thirteen occurred after parturition. This is of real but as yet undetermined significance, especially in the light of the freedom from exacerbations in all patients in whom interruption of their pregnancies, either spontaneously or by induction, occurred before term. It is therefore felt that pregnancy has no demonstrable effect on the over-all incidence of exacerbations in Hodgkin's disease. If there is any tendency whatsoever for exacerbations in Hodgkin's disease to occur during pregnancy, they most likely follow delivery at term. It is therefore considered that there is little evidence from this study to advocate interruption of pregnancy during the course of Hodgkin's disease. When specific and definite obstetrical indications for interruption of pregnancy not related to the Hodgkin's process are present, there is certainly no contraindication to interruption of pregnancy as far as the Hodgkin's disease is concerned.

On the other hand, Hodgkin's disease has little or no effect on the occurrence, course, duration, complications, or end results of gestation.

Conclusions

1. Hodgkin's disease complicating pregnancy does not grossly affect ovulation, fertility, incidence of spontaneous abortion, ante-, intra-, or postpartum hemorrhage.

2. The obstetric aspects of gestation, parturition, and the puerperium are not affected by coincidental Hodgkin's disease.

3. Hodgkin's disease is transmitted from the mother to the fetus across the placenta in 9 per cent of reported cases.

4. There is no report in the literature of injury to the shielded fetus from roentgen radiation used in the treatment of Hodgkin's disease.

5. Interruption of pregnancy during the course of Hodgkin's disease is not indicated from the evidence at hand.

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INDICATIONS FOR HORMONAL PELLETS IN THE THERAPY OF ENDOCRINE AND GYNECIC DISORDERS*

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IT HAD been noted by many investigators in both animal and clinical experimentation that implantation of hard compressed pellets of crystalline steroids resulted in a slow and more physiologic absorption of the hormone than that observed after parenteral administration. Since the amount of the hormone released to the organism is continuous though minute in quantity, it is conceivable that by this method the endogenous mechanism of hormonal secretion is more nearly approached and the physiologic action of the hormone more closely imitated.[1-6] In 1942 Corner[7] predicted that, "pellets will probably be used in human cases in which long continued action is required, not only because of the continuous absorption, but also because insertion of the pellet, which can be done through a hollow needle, avoids repeated hypodermic punctures."

The numerous objections to the repeated parenteral administration of hormonal preparations are apparent to both physician and patient. The implantation of hormonal pellets may be undertaken in a great variety of conditions requiring prolonged hormonal therapy. Besides eliminating the necessity and inconvenience of frequent injections, the economy of this mode of therapy places it within reach of most patients. Satisfactory results may be obtained for periods up to six months and longer.

Technique of Pellet Injection

With the use of the Kearns Pellet Injector (Fig. 1), the disadvantages of previous methods of subcutaneous and subfascial pellet implantation have been largely eliminated. Implantation by these earlier methods was followed by expulsion of the pellet in as many as 15 per cent of cases, whereas, with the Kearns instrument pellet extrusion is rarely seen, and in our experience, occurred in less than 2 per cent. In those instances in which the pellets were recovered after varied periods, and weighed, it was found that absorption closely followed the more or less constant curves previously reported.[8, 9]

An area of skin is chosen on the anterior abdominal wall about one inch medial to the anterior superior spine of the iliac crest, on either the right or left side. The skin is cleansed with any of the accepted antiseptic preparations, and then anesthetized with 1 or 2 c.c. of a 2 per cent solution of procaine hydrochloride (Fig. 2). The sterilized pellet injector with stylet in place is directed parallel to the inguinal ligament, and inserted subcutaneously to the depth of the first bolt (Fig. 3). The stylet is removed, and the pellet placed in the groove at the exposed end of the hollow needle. Care should be taken when placing

*This work was aided by a grant from Schering Corporation, Bloomfield, N. J. Supplies of pellets of estradiol, testosterone (Oreton-F), progesterone, and desoxycorticosterone acetate (Cortate) were made available through the courtesy of Dr. W. H. Stoner and Dr. Edward Henderson of Schering Corporation.

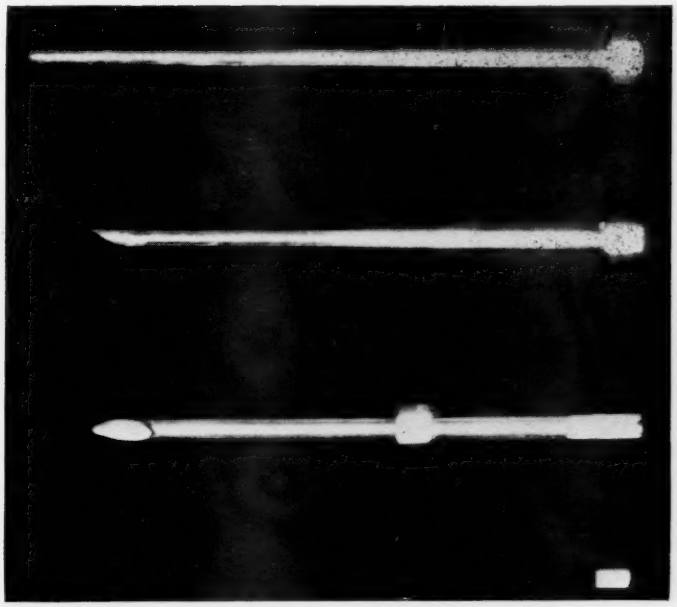

Fig. 1.—The Kearns Pellet Injector (unassembled) with pellet.

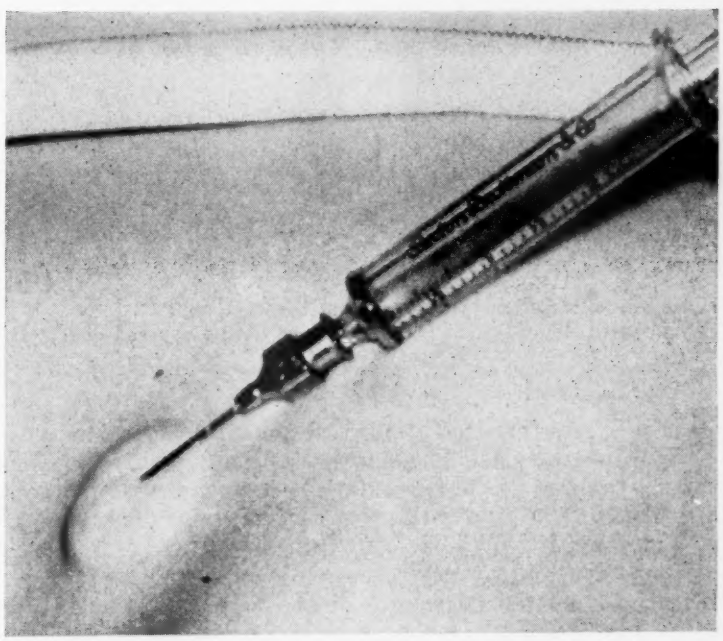

Fig. 2.—Anesthetizing the skin with procaine hydrochloride solution.

the pellet into the cannula, as the pellet cannot be re-sterilized if it falls out and becomes contaminated. By holding the sterile tray beneath the groove, the pellet will be caught in this tray, and can be replaced (Fig. 4). As many pellets as indicated may be added. Twelve pellets have been implanted by a single injection. The blunt plunger is then fully inserted, gently pushing the pellets into the subcutaneous tissues. The instrument is withdrawn, and a dry dressing placed over the wound. The pellets may be palpated in the subcutaneous tissues of the anterior abdominal wall, just above the middle of Poupart's ligament.

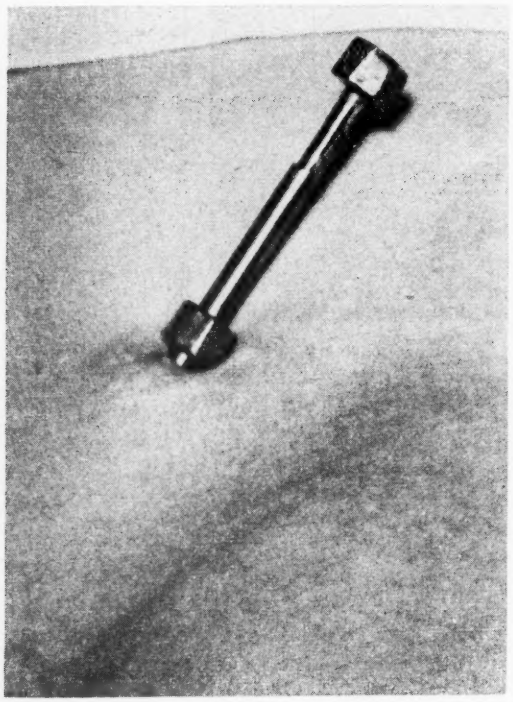

Fig. 3.

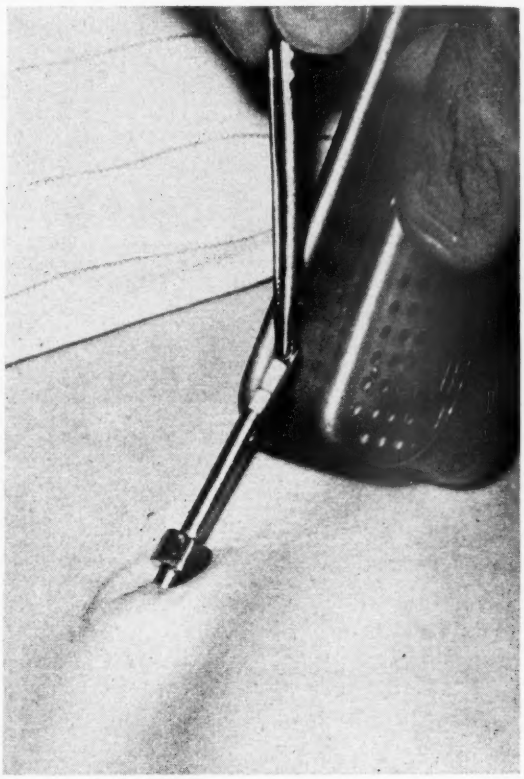

Fig. 4.

Fig. 3.—Subcutaneous insertion of the cannula with stylet.
Fig. 4.—Introduction of the pellets into the groove at the exposed end of the cannula.

Absorption

If pellets are manufactured under standard conditions, i.e., uniformly compressed crystalline material, it holds that pellets of greater weight will be of proportionately greater size. The rate of absorption, per pellet, will depend on its surface area. The percentage of absorption of each weight group of pellets will follow its own definite curve. The total rate of absorption on any given day or any given time depends on the number of pellets implanted and not on the actual weight of the pellets. Since pellets of similar size are more or less absorbed at moderately uniform rates, and since the rate of absorption depends on the number of pellets and the surface area, the following hypothesis may be in order: "The rate of absorption of any given amount of crystalline hormone depends on the number of pellets implanted at one time and not on the size or weight of the pellets, and the time that the

pellets continue to give off appreciable material depends on the size and weight of the pellets implanted.''[10] The manner of absorption is mainly a physical phenomenon depending on the surface area exposed to the dissolving action of tissue fluids. Influencing factors are the density of the pellet, the size of the particles (crystals) that comprise the pellet, and the site of implantation.[8]

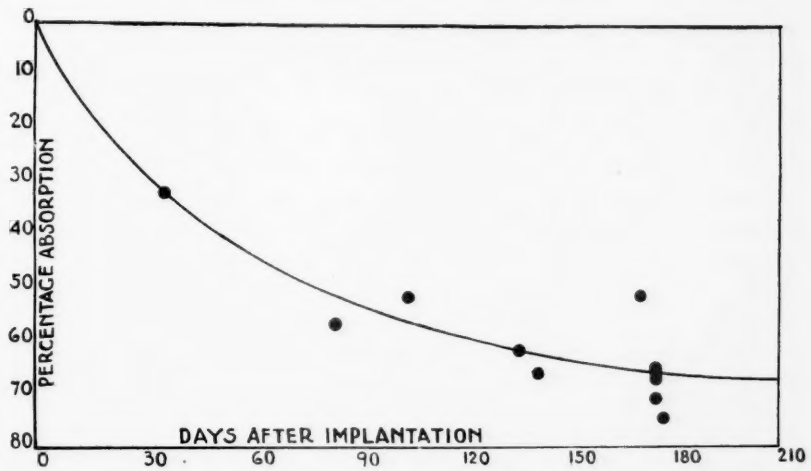

Fig. 5.—Percentage mean absorption curve for 100 mg. pellets of testosterone propionate. (From: Greenblatt, R. B., and Hair, L. Q.: J. Clin. Endocrinol. 2: 315, 1942.)

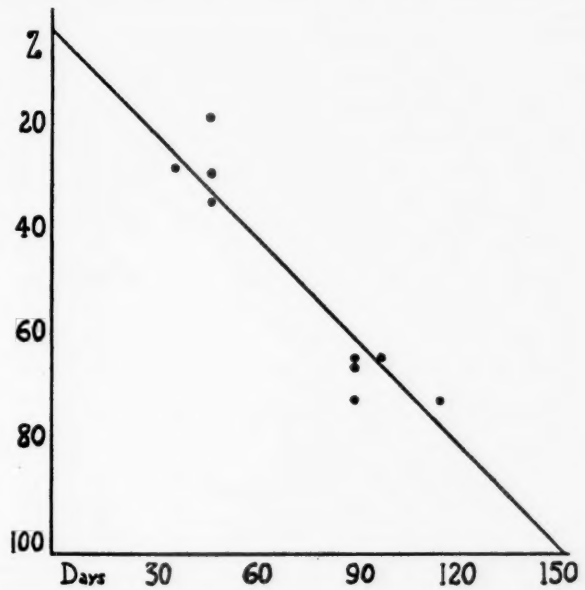

Fig. 6.—Percentage absorption of 50 mg. pellets of progesterone. (From: Greenblatt, R. B., and Hair, L. Q.: J. Clin. Endocrinol. 5: 38, 1945.)

When the percentage absorption is plotted against the number of days that the pellets remain in situ, the resultant curves are more or less smooth with the individual deviations of each weight group being only moderate in extent. The percentage of absorption during the first month is relatively rapid for all groups. The rate of absorption progressively decreases with each suc-

ceeding month, the curve tending to level after the hundredth day. The decrease in rate of absorption is inversely proportional to the surface of the pellet. Fig. 5 shows the percentage mean absorption curve for 100 mg. pellets of testosterone propionate.[8] Fig. 6 shows the percentage absorption of 50 mg. pellets of progesterone.[9]

Indications for the Use of Pellets

Estradiol Pellets (25 mg. in weight).—

1. In patients with severe menopausal syndrome in whom prolonged injections of estrogens are necessary.
2. In young women with hypoplasia of uterus or breasts.
3. Dysmenorrhea associated with hypoplasia of the uterus.

Note: Estradiol pellets are contraindicated in patients with a history of cancer or with so-called precancerous lesions. It is preferable that estradiol pellets should not be used except in those patients without uteri.

Progesterone Pellets (50 mg. in weight).—

1. May be used along with estrogens in the treatment of menopausal patients.
2. In selected patients with nervous tension states.
3. Nymphomaniacal tendencies that prove distressing.
4. In treatment of habitual abortion.[11]
5. In treatment of puberal breast hypertrophy.[9]

Note: Combined estradiol-progesterone pellet implantation should never be used in the menopausal patient with an intact uterus, as prolonged bleeding usually ensues.

Testosterone Pellets (75 mg. in weight).—

1. In certain patients with symptoms of menopausal syndrome in whom estrogen therapy has proved unsatisfactory or is contraindicated.
2. In combination with estradiol pellets in patients with uteri who have severe menopausal symptoms, in order to prevent the untoward bleeding induced by estrogens.[12]
3. The dysmenorrheic patient with possible endometriosis or small fibroids.
4. The patient with fibromyomata for whom surgery is not feasible.
5. The patient with nocturia of endocrine origin.[13]
6. The female who is not psychologically frigid and in whom increased libido is desirable.[14]
7. As a palliative measure in patients with advanced carcinoma of the breast.
8. In combination with desoxycorticosterone pellets for Addison's disease.

Note: Testosterone pellets should not be used in women who have a tendency toward acne or hirsutism.

Desoxycorticosterone Acetate Pellets (75 mg. in weight).—

1. Addison's disease.[15]
2. In panhypopituitarism, pellets of desoxycorticosterone acetate may be implanted along with testosterone.
3. In certain asthenic patients who have low blood pressure, low blood sugar, and marked fatigability, it appears that this form of medication proves helpful.

Note: Desoxycorticosterone is contraindicated in hypertension or heart disease.

Typical Case Reports

Climacteric.—

(1) *Estradiol Pellets:* D. E., a 56-year-old white woman, was seen in April, 1947. Hysterectomy had been performed in 1936. During the preceding seven years, the patient

had frequent hot flushes, cried easily, was unable to concentrate, and stated that her memory was poor. Her emotions were easily disturbed. She had received repeated courses of estrogen therapy, orally and parenterally, with only partial alleviation of symptoms. In April, 1947, two 25 mg. pellets of estradiol were implanted. Improvement was noted almost immediately. The hot flushes were practically eliminated. Her emotions stabilized, she was more receptive to visitors, and her attitude to life in general was greatly improved. Her symptoms have remained under control for a period of ten months.

(2) *Estradiol and Testosterone Pellets:* B. B., a 50-year-old white woman, was first seen Aug. 22, 1942, complaining of frequent, severe hot flushes, nocturia, nervousness, backache, headaches, and paresthesia. Menses had ceased three years previously. During the following five years the patient was treated with estrogens, progestogens, and androgens, given orally and parenterally, with unsatisfactory results. On October 6, 1947, the patient's complaints were particularly severe. At this time two 25 mg. pellets of estradiol, and one 75 mg. pellet of testosterone were implanted. Improvement was noted shortly. She experienced almost complete relief of all symptoms, and her complaints have been satisfactorily controlled during the six months' follow-up to date. No untoward bleeding occurred.

(3) *Estradiol, Progesterone, and Testosterone Pellets:* B. J., a white woman aged 41 years, was seen on Nov. 14, 1946. Her uterus, tubes, and ovaries had been surgically removed in 1939. The patient complained of fatigue, emotional instability with nervousness, and extreme depression, formication, and occasional hot flushes. She was treated with oral estrogens for several weeks, and showed some improvement. On Jan. 13, 1947, one 25 mg. pellet of estradiol, one 50 mg. pellet of progesterone, and one 75 mg. pellet of testosterone were implanted. She was seen the following month and stated that her symptoms were completely ameliorated. The symptoms remained under control for six months. On July 3, 1947, the patient returned, and reported that there was a decline in her well-being. One 25 mg. pellet of estradiol, and one 75 mg. pellet of testosterone were implanted. She remained in good health during the next six months, but noted somewhat less improvement than following the first series of pellets. She returned on Jan. 9, 1948, because some of her symptoms were becoming manifest, however slight. She feared a recurrence, and requested a repeat implantation. One 25 mg. pellet of estradiol, one 50 mg. pellet of progesterone, and one 75 mg. pellet of testosterone were again implanted. Her complaints were again quickly relieved, and she has remained in good health to date.

Habitual Abortion.—

Estradiol and Progesterone Pellets: J. W., a gravida v, para i, white woman aged 43 years of age, was seen June 5, 1946, with a history of three abortions following the birth of her first child in 1936. Each abortion occurred between the second and third months of gestation. She also had one abortion prior to the first child. At the time of her visit, the period was approximately one week overdue, the date of the last menstrual period being April 28. Examination suggested pregnancy, and the pregnancy test was reported positive. Two 25 mg. pellets of estradiol, and three 50 mg. pellets of progesterone were implanted. The patient was kept at bed rest until the seventh month of gestation. Thyroid and vitamin E were prescribed. During the fifth, sixth, and early part of the seventh months, 5 mg. of progesterone were given by injection twice weekly. At no time during the course of pregnancy was there any evidence of threatening abortion. The patient was delivered of a normal, 7¼ lb. female infant on Jan. 30, 1947.

Loss of Libido.—

Testosterone Pellets.—G. P., a white female of 31 years was seen on May 30, 1946. She had been married for 12 years, but had no children. She complained of nervousness, backache, severe headaches, insomnia, and swelling of feet and ankles. She had not menstruated during the preceding year, although previously the menses had been regular. Her libido was markedly diminished. Examination revealed an infantile uterus. Suction curettage was performed, and the endometrium was atrophic. The vaginal smear showed mostly basal cells. A diagnosis was made of precocious menopause, with marked reduction of libido. The patient was treated with stilbestrol, thyroid, and vitamin B for three weeks, with only slight improvement. On July 11, 1946, two 75 mg. pellets of testosterone were implanted.

She was seen again August 22, and stated that her condition was greatly improved. Headaches had ceased, she slept well, and her libido was definitely increased. Examination showed the clitoris to be slightly enlarged, and very sensitive. The patient returned March 11, 1947, and stated that symptoms had been adequately controlled for seven months, but recently her well-being and libido had lessened. Two 75 mg. pellets of testosterone were again implanted. There was immediate improvement, and her complaints were controlled for an additional period of five months. She was seen on Sept. 19, 1947, complaining of a recent decrease in libido. Two 75 mg. pellets of testosterone were implanted. Libido was restored, and remained at a high level for five months. She was last seen on Jan. 24, 1948, at which time one 25 mg. pellet of estradiol, and one 75 mg. pellet of testosterone were implanted in order to maintain her well-being and clinical improvement.

Endometriosis.—

Testosterone Pellets: E. S., a 24-year-old white woman, complained of dysmenorrhea for the duration of the menses so severe that her physician had to resort to some opiate for relief. Following the cessation of flow, pain in the left side persisted for one week afterward. Examination revealed a retroverted adherent uterus, with tenderness and some fullness of the left fornix. A diagnosis was made of endometriosis. In 1943, complete relief was afforded for a period of six months by injections of testosterone propionate, 25 mg. every fifth day. Two months after the injections were discontinued, the pain returned. Therapy was resumed, and continued for eight months with amelioration of her syndrome. In April, 1946, the patient complained of excruciating pain in the left side for one week following menstruation. She had noticed burning on urination when the pain was present. The patient stated that she was relieved of the dysmenorrhea. At this time urologic consultation was sought, and the urologist concurred in the diagnosis of endometriosis. It was felt that the pain was produced by an endometrioma causing pressure on the ureter. Three 75 mg. pellets of testosterone were implanted. The pain was relieved for six months, but recurred following the next menstrual period. Pelvic examination showed the uterus still retroverted, but slightly more moveable. There was tenderness in the left fornix; and some induration of the left uterosacral ligament. Three 75 mg. pellets of testosterone were again implanted. There was no pain following menstruation in December. The patient became pregnant, but aborted in February, 1947. Shortly thereafter, she became pregnant again, and was delivered on Nov. 29, 1947, of a normal male infant.

Addison's Disease.—

Desoxycorticosterone and Testosterone Pellets: R. C., a 31-year-old white nullipara, was first seen in September, 1946. Her complaints were extreme weakness, headaches, marked generalized pigmentation especially of face and upper extremities, and partial loss of head, axillary, and pubic hair. The diagnosis of Addison's disease was confirmed by laboratory tests. At this time three 75 mg. pellets of desoxycorticosterone were implanted. Aqueous adrenal cortical extract was prescribed in 1 c.c. doses twice weekly. Extra salt was added to the diet. During the following three months the patient improved rapidly. On Dec. 12, 1946, one 75 mg. pellet of desoxycorticosterone was implanted. Improvement continued, and in May, 1947, three 75 mg. pellets of desoxycorticosterone, and two 75 mg. pellets of testosterone were implanted. The patient continued to do well. She gained weight, did not fatigue easily, hair growth was restored, and pigmentation decreased somewhat. On Aug. 12, 1947, one 75 mg. pellet of desoxycorticosterone, and one 75 mg. pellet of testosterone were implanted. The patient was last seen on Feb. 4, 1948. At this time she stated that she had not taken any adrenal cortical extract or extra salt for the past four months, and that she felt extremely well.

Summary

The implantation of hormonal pellets has proved of value in the management of a great variety of endocrine and gynecic disorders. Pellet implantation is indicated in those conditions where prolonged hormonal therapy appears necessary. With the use of the Kearns Pellet Injector, pellet implantation is a simple office procedure. Some of the indications and contraindications

for pellet implantation are listed. A number of typical case reports are cited in which pellet implantation was of definite benefit to the patient. It appears that the pellet method of hormone administration has more nearly approached the endogenous rate of hormonal secretion. Furthermore, its use has made possible a clearer understanding of the physiologic properties of certain steroids.

Testosterone and desoxycorticosterone acetate pellets are now commercially available, and it is hoped that pellets of estradiol and progesterone will soon be made available for general use.

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MORPHINE SUPPRESSION OF URINARY OUTPUT IN PREGNANT AND NONPREGNANT WOMEN

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THE effect of morphine on urinary output has been a controversial subject[1-4] as indicated in a review of the literature by Ferrier and Sokoloff.[5] These authors presented evidence of the antidiuretic action of morphine and Demerol in patients with congestive heart failure. In 1944 and 1945, the antidiuretic effect of morphine in dogs was described by DeBodo,[6, 7] who concluded that this effect was due to release of antidiuretic principle from the neurohypophysis. In further experiments, it was shown that phenobarbital, Sodium Amytal and pentobarbital also had this antidiuretic effect but to a lesser degree, depending upon the dosage given.

The studies here presented began in May, 1947, shortly after an apparent suppression of urinary output was noted following the administration of morphine to several patients with eclampsia or severe pre-eclampsia. It was decided to determine the effect of a single injection of morphine on the urinary output of normal pregnant and nonpregnant women.

Method

The pregnant patients were in the last trimester of uncomplicated pregnancies. The nonpregnant individuals had entered the hospital because of uncomplicated vaginal prolapse, sterility, or for sterilization. Various age groups were represented. Most of the studies were carried out before operation but a few were done after the seventh day of a normal afebrile postoperative convalescence.

During the evening before the first experimental day, the patient was instructed to drink at least 500 c.c. of water before midnight. Thereafter, she took nothing by mouth for the next sixteen hours. At 8 A.M., an indwelling catheter was inserted and the urine obtained was discarded. An intravenous infusion of 2,400 c.c. of 5 per cent dextrose in distilled water was begun and the rate of flow regulated so that this volume would be administered during a five-hour period. The urine was collected as eight consecutive hourly specimens from 9 A.M. until 4 P.M. The next sixteen-hour output was collected as a single specimen except for the initial series of nine patients from whom only the eight hourly specimens were obtained. During this sixteen-hour period the patient was offered a full liquid diet.

The procedure was duplicated on a control day and a test day with at least forty-eight hours intervening. The only variable between the two days was the injection of morphine on the test day. In three instances the morphine day preceded the control day. The morphine sulphate, ¼ grain (16 mg.), was given intramuscularly at the time the intravenous fluid was started. In a few patients, less than 2,400 c.c. of fluid was given intravenously; however, the fluids were

carefully measured and the same volume at approximately the same rate was given on the next test day. Thus, while volumes varied slightly, the volume and rate of intake in the same patient were equal on both days.

Only the urine volume and specific gravity were noted on the first nine patients. In a second group of six normal patients, four pregnant and two non-pregnant, the urine was collected over the twenty-four hour period as described. In addition, hematocrit determinations were made at the beginning and end of the initial eight-hour period. Blood pressures and pulse rates were recorded hourly for eight hours beginning at 8 A.M. on the experimental day. In addition to volume and specific gravity, determinations of chloride concentration were also made for each of the nine specimens.

The preliminary chloride intake was that of the general hospital diet which contains 4 to 5 Gm. of sodium chloride daily. The full liquid diet contained 5 to 6 Gm. of sodium chloride per day.

In a few patients who reacted to the infusion with chills and fever, the experiment was discontinued and the record discarded. Occasionally, nausea and vomiting necessitated discontinuing the infusion late in its course. In most instances, the emesis volume was accurately measured and included in the output volume.

Observations

The results obtained on the initial group of nine patients are shown in Table I. In all instances, the injection of morphine caused a decrease in urinary volume. In two cases, the total eight-hour urinary excretion was not appreciably diminished but hourly output was diminished during the maximal clinical effect of the morphine, with a compensatory increase during the last two or three hours.

The average summation curves for all the patients in this group are shown in Fig. 1. The total eight-hour urine output on the morphine days averaged 48 per cent of that on the control days. In Fig. 2, the average hourly output is represented. It is interesting to note that the increased urine volume during the first hours of the infusion was followed by a decreasing output even though fluid intake continued at a constant rate.

TABLE I. NORMAL WOMEN ARE REPRESENTED. THE TOTAL EIGHT-HOUR URINARY VOLUME FOR THE CONTROL PERIOD IS COMPARED WITH THE VOLUME OBTAINED AFTER INJECTION OF ¼ GRAIN (16 MG.) MORPHINE SULPHATE

PATIENT	AGE	WEIGHT IN LBS.	TOTAL OUTPUT IN C.C.	
			CONTROL DAY	MORPHINE DAY
I. J.	17	105	1965	1625
S. P.	26	154	1889	1633
M. D.	35	152	1980	523
P. G.	49	150	1160	722
E. H.	52	171	1905	351
C. R.	56	166	2145	1205
M. H.	61	152	2335	482
E. W.	61	177	1725	1005
A. K.	73	163	2540	1025
		Average:	1960	952

Studies on the second group of patients were postponed until October, 1947, in order to avoid the hot summer months when insensible water loss might be excessive. In this group of six patients, the observations covered a twenty-four-hour period as previously described. The group included four pregnant women and two patients from the gynecologic service. In all instances, the urinary output was suppressed for eight hours on the morphine day but later there was a compensatory increase so that the total twenty-four-hour volume approached that of the control day. (Table II.)

The hematocrit readings done at 8 A.M. and 4 P.M. on each test day showed no evidence of any blood dilution. This would indicate that the retained fluids were extravascular. Blood pressures and pulse rates were recorded every hour for eight hours but the average values and the deviations were not significantly different on the two days.

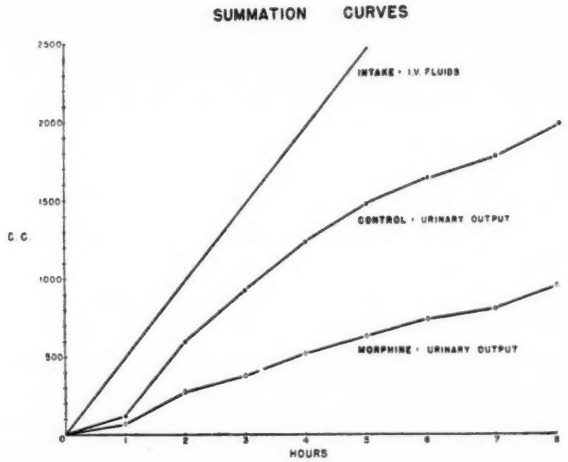

Fig. 1.—Summation curves of the average eight-hour urinary outputs obtained on nine women. 2,400 c.c. 5 per cent dextrose were given intravenously at a constant rate over five hours. On morphine day, morphine sulfate, ¼ grain (16 mg.), was given intramuscularly at the start of the infusion.

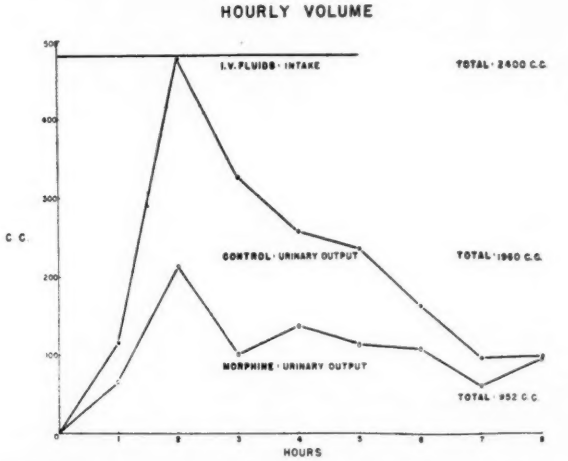

Fig. 2.—Average hourly urine volumes on same group of nine women as are represented in Fig. 1.

Urinary chloride concentrations were determined on each of the eight hourly specimens and the sixteen-hour specimen. The total chloride was calculated for each specimen and for the total twenty-four hours. The results, expressed as grams of sodium chloride, are shown in Table II and in Figs. 3 to 6.

In four of the six patients, there was a definite decrease in total urinary chlorides on the morphine day. The concentration of chloride in the urine was not consistently increased on the morphine days as compared to the control days. Thus the low concentration of chloride together with the decreased urinary volume resulted in a decreased total chloride output on the morphine

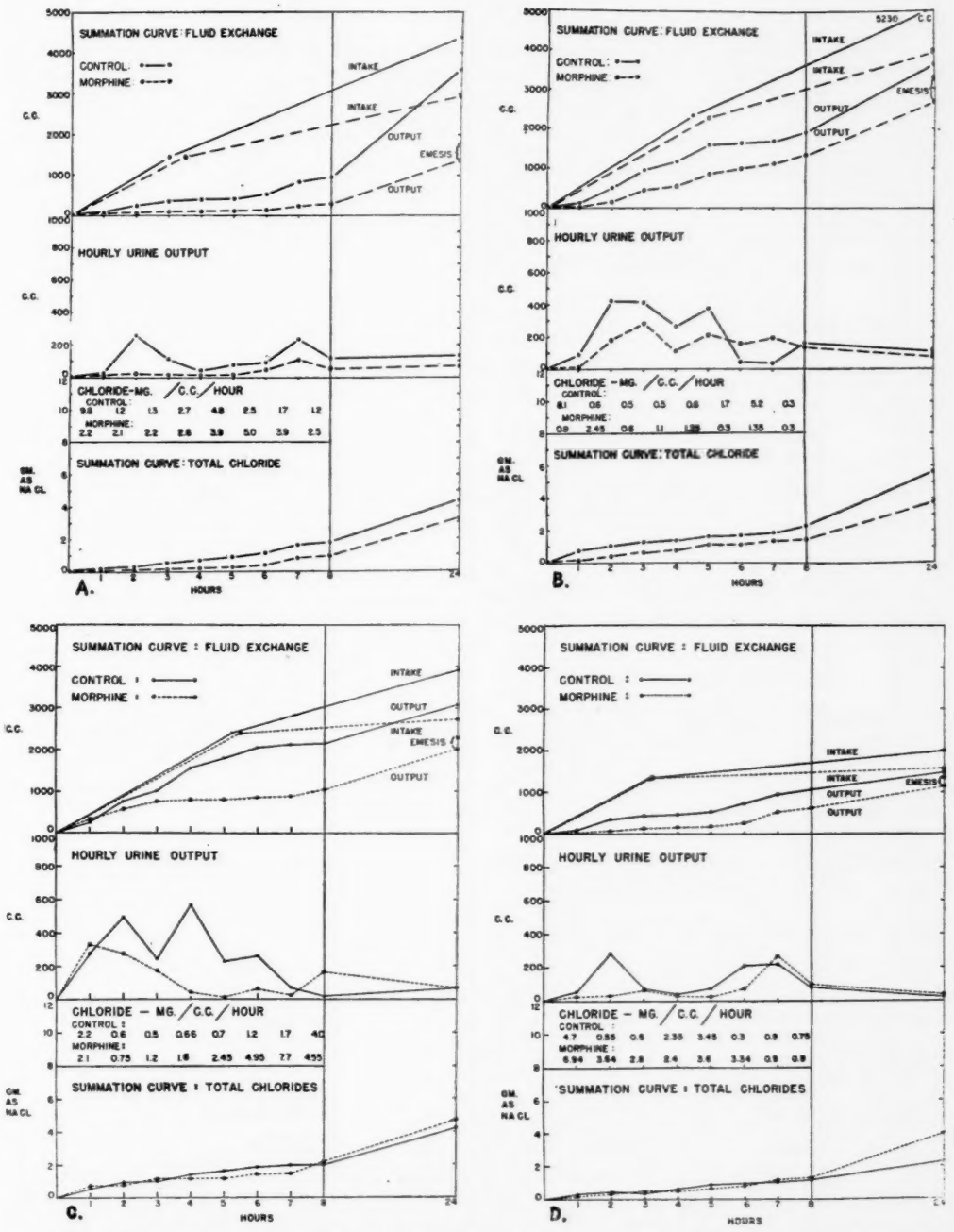

Fig. 3.—Graphic representation of results obtained on four normal pregnant women. Hourly urine specimens were collected for the first eight hours and a single specimen for the next sixteen hours. Fluid exchange is represented as intravenous and oral intake against urinary output. The insert represents chloride concentration in each of the first eight hourly specimens. *A.* G. W., aged 32 years, seven months pregnant. *B.* R. M., aged 27 years, seven and one-half months pregnant. *C.* B. V., aged 18 years, seven months pregnant. *D.* M. B., aged 19 years, six and one-half months pregnant.

days. The low chloride concentrations were correlated with comparably low specific gravities, indicating that the urinary solutes remained low even during the period of diminished urine volume.

This is contrary to the results obtained by DeBodo on dogs,[7] in which he reported a fiftyfold increase in chloride concentration and a twofold increase in total chlorides excreted in the first three hours after giving morphine.

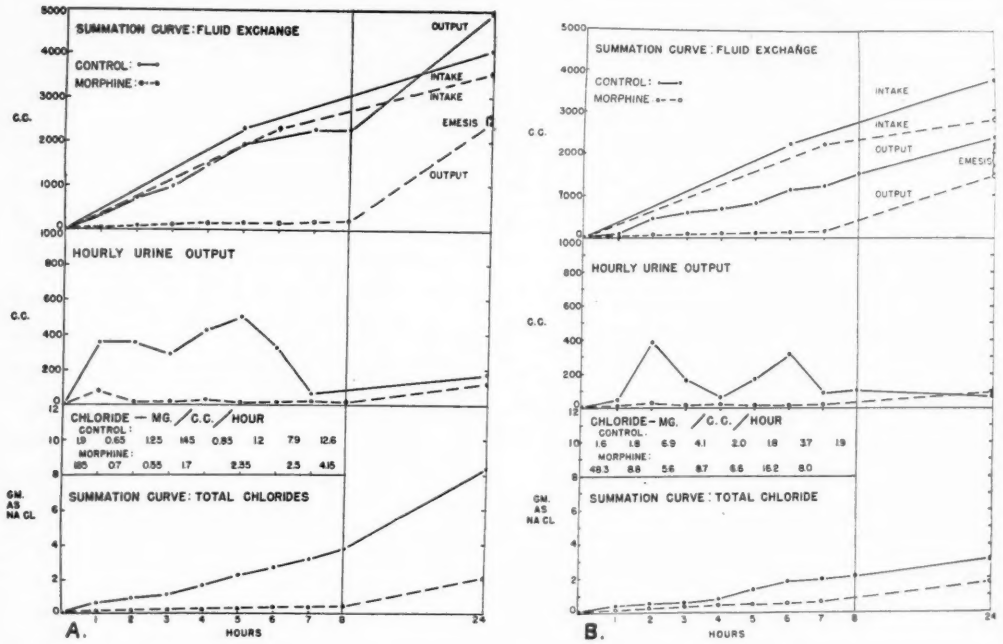

Fig. 4.—Graphic representation of the results obtained on two normal nonpregnant women observed under the same conditions as the pregnant patients represented in Fig. 3. *A*. E. S., aged 33 years. *B*. E. M., aged 29 years.

TABLE II. THE INTRAVENOUS FLUID VOLUME, TIME OF ADMINISTRATION, AND THE EFFECT OF MORPHINE OR PITRESSIN ON FLUID OUTPUT AND CHLORIDE EXCRETION IN PATIENTS SHOWN IN FIGS. 3, 4, AND 5

PATIENT	AGE	DAY	INTRAVENOUS 5 PER CENT DEXTROSE: TOTAL C.C.	INTRAVENOUS 5 PER CENT DEXTROSE: TIME HR.	URINE VOLUME IN C.C.: 8 HR.	URINE VOLUME IN C.C.: 24 HR.	TOTAL CHLORIDES IN GM.
Normal Pregnant Women in Third Trimester							
R. M.	27	Control	2300	4½	1821	3671	5.5
		Morphine	2300	4½	1312	3332	3.7
B. V.	18	Control	2400	5½	2141	3091	4.2
		Morphine	2400	5½	1050	2285	4.7
G. W.	32	Control	1400	3	938	3678	4.4
		Morphine	1400	3	273	1683	3.2
M. B.	19	Control	1350	3½	1064	1495	2.2
		Morphine	1350	3½	615	1378	1.2
		2 units Pitressin (H)	1400	3¼	1155	2025	5.2
Normal Nonpregnant Women							
E. M.	29	Control	2200	6½	1297	2337	3.0
		Morphine	2200	6½	65	2165	1.0
E. S.	33	Control	2300	5½	2352	4952	8.4
		Morphine	2300	5½	209	2404	2.0
M. S.	19	Control	2400	5	2915	3088	7.0
		0.5 c.c. Pitressin tannate in oil	2400	5	813	1623	10.7

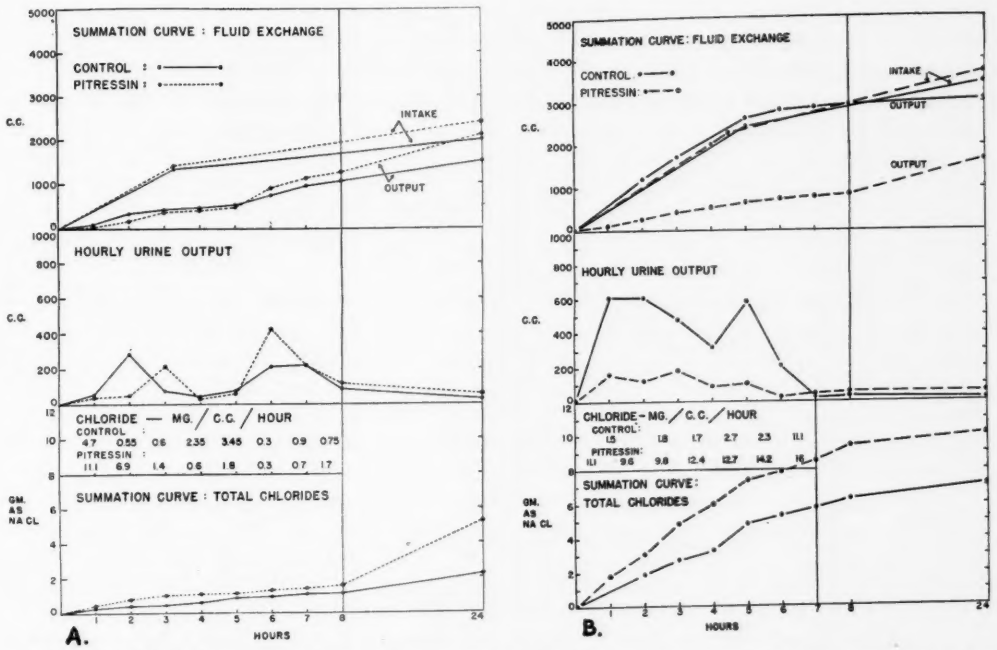

Fig. 5.—Graphic representation of the results obtained on two women, one pregnant, who were given Pitressin instead of morphine and the results are compared with the control day. *A*. M. B., aged 19 years, six and one-half months pregnant. Patient given 2 units aqueous Pitressin at 8 A.M. Compared with Fig. 3*D* which represents effect of morphine on the same patient. *B*. M. S., aged 19 years. Patient given 5 units of Pitressin tannate in oil at 8 A.M.

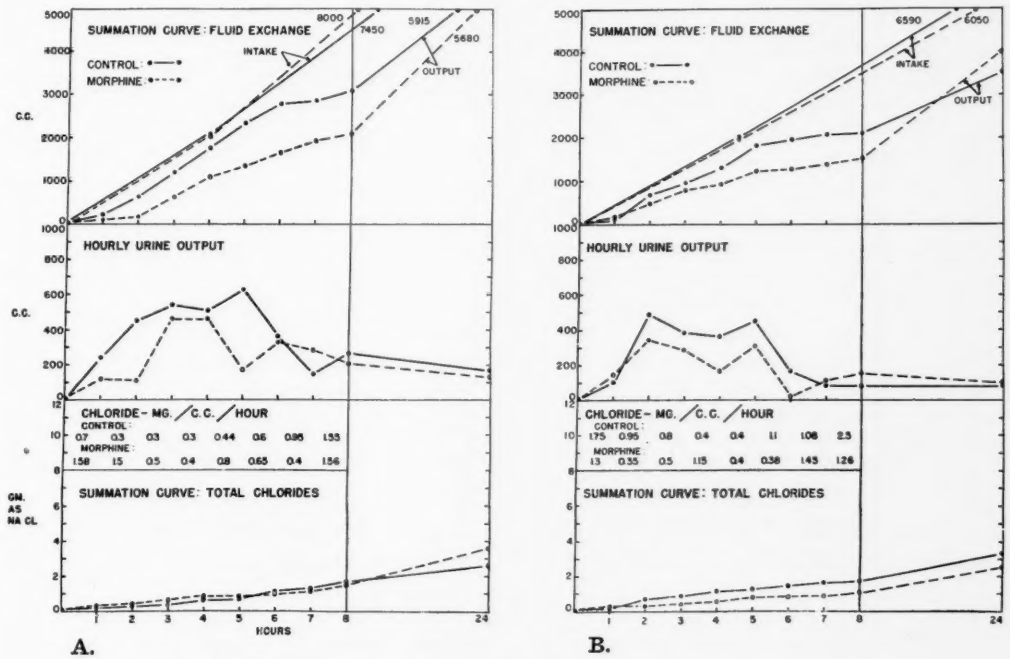

Fig. 6.—Graphic representation of the effect of morphine in two women with diabetes insipidus presented for comparison with its effect on normal women, Figs. 3, 4, and 5. *A*. L. B., aged 26 years. *B*. M. D., aged 62 years.

Further observations were believed necessary to determine whether the release of posterior pituitary hormone is the cause of the antidiuretic effect of morphine. After DeBodo had determined the action of morphine in dogs, he injected Pitressin into normal animals and noted a marked similarity in the results. This was the next step in our observations on the human being.

In two patients, injections of Pitressin were substituted for morphine in order to compare their antidiuretic action. One patient (M. B., aged 19 years), in the third trimester of a normal pregnancy, was given 2 units of aqueous Pitressin, while the other (M. S., aged 19 years) received 5 units of Pitressin tannate in oil.

The patient receiving the aqueous Pitressin demonstrated little suppression of urine output except during the first three hours following the injection. (Fig. 5*A*.) However, the urinary chloride concentration increased markedly and total twenty-four-hour chloride output was increased from 4.0 Gm. (on control day) to 5.27 Gm. The same patient on a morphine day (Fig. 3*D*) had urinary suppression and also showed a decrease of total chlorides to 2.2 Gm. as compared to 4.0 Gm. on control day.

The second patient (Fig. 5*B*), who was given Pitressin tannate in oil, had marked suppression of urinary output over the entire twenty-four-hour period as compared with the control day. However, in spite of the urine suppression, the chloride concentration on the Pitressin day was so high that the total chloride output was 10.8 Gm. as compared to 7.0 Gm.

The results obtained with injection of Pitressin in human beings confirmed the findings in dogs. However, the similar action of Pitressin and morphine in dogs could not be demonstrated in women.

DeBodo also presented the results of morphine given to dogs with diabetes insipidus (stalk-sectioned). He found that the antidiuretic action of morphine was abolished in this group. While it is not possible to determine the exact amount of posterior pituitary still functioning in patients with diabetes insipidus, these individuals offer the only means of comparison with the stalk-sectioned laboratory animal. Two patients with diabetes insipidus were observed, using the same methods as with the normal control groups. The diabetes inspidius was confirmed in both patients before any test days were observed. (See Appendix.)

The urine outputs of the two patients with diabetes insipidus (Figs. 6*A* and 6*B*) were suppressed on the morphine day but to a lesser degree than in most of the normal patients. In patient L. B., the chloride concentration and total chloride output during the first eight hours was approximately the same on the two days. The total chloride excretion on the morphine day increased slightly over that of the control day in the subsequent sixteen-hour specimen. In patient M. D., the urinary chloride concentration and the total chlorides were decreased during the morphine test.

These observations thus demonstrated a urinary suppression caused by morphine in two patients with long-standing diabetes insipidus. Since this suppression occurred in spite of reduced output of the antidiuretic principle of the posterior pituitary, it appears that the action of morphine is not mediated by the antidiuretic hormone. This is additional evidence that the effect observed by DeBodo is not the same as that which occurs in human beings.

Discussion

The one constant result obtained in this series of observations was the suppression of urinary output after a single injection of morphine. The degree of suppression varied from patient to patient, with the age factor appearing to be most important. In general, the younger the patient, the less the suppression. This was probably due to the degree of tolerance to morphine. The

clinical narcotic effect of morphine was approximately the same in all age groups, but the younger patients recovered more rapidly. No attempt was made to regulate the dose of morphine in proportion to body weight, nor was the intravenous fluid intake so regulated. The purpose was to determine the effect of a single one-quarter-grain (16 mg.) injection of morphine, and the fluid (5 per cent dextrose) was given intravenously in approximately the rate and amount which might be used clinically.

Since it was not possible to control as many factors as DeBodo did in the dog, the only possible comparison involves the urinary output and the urinary chlorides. Our findings agree that suppression occurs, but neither the chloride concentration nor the total chloride output was elevated as found by DeBodo in dogs. In most instances the total chlorides were decreased. However, it must be pointed out that the doses of morphine used by DeBodo greatly exceeded those used on the human being in this series. It is not known what the effect of greater doses or repeated doses of morphine would be in the human subject.

In the two patients, one pregnant and one nonpregnant, who received Pitressin, there was a marked increase in urinary chloride concentration on the Pitressin day as compared with the control day. This result can be compared with the morphine day in the pregnant patients when there was a decrease of total chloride and in chloride concentration as compared with the control day. This again indicates that a mechanism other than the posterior pituitary is acting to cause urinary suppression.

In the two patients with long-standing diabetes insipidus, Pitressin injections were withheld until the symptoms of the disease entity had become reestablished. In both patients, the urinary volumes were suppressed on the morphine day. The chloride concentration and the total urinary chlorides were about equal in one patient while both the concentration and total values decreased in the other. Again evidence was adduced pointing away from the mediation of the morphine effect through the neurohypophysis.

A finding, which was incidental to the main purpose of the experiments, but which evoked considerable interest, was the effect of the prolonged intravenous infusion of 5 per cent dextrose on the urinary output during control days. Little was found in the literature to explain why the initial diuretic surge during the first hours was followed by a rapid drop in output and a smaller secondary rise at about the fourth hour. This typical pattern can be seen on the figures showing the hourly urine outputs. The significance of this pattern is not known, but should be studied further. Verney,[9] in discussing the antidiuretic hormone and its release in the dog, showed that intravenous hypertonic solutions of dextrose resulted in a release of antidiuretic substance and a drop in urinary output. "Osmoreceptors" present somewhere in the vascular beds of the internal carotid arteries are sensitive to osmotic pressure changes and can cause a release of antidiuretic hormone from the neurohypophysis. Whether a similar mechanism might be induced with prolonged intravenous administration of 5 per cent dextrose is yet to be determined.

Ferrier and Sokoloff reported an antidiuretic effect of morphine in congestive heart failure. The fact that their patients were given 3 Gm. of ammonium chloride daily and received a mercurial diuretic makes it difficult to

interpret the results. Their findings on four normal control patients showed an increase of total urinary chlorides in two instances but the morphine negated the effect of the mercurial in the other two. In the patients with cardiac failure, the total urinary chlorides remained the same or decreased. The decrease in urinary output was not a constant finding. In none of our normal patients was the total urinary chloride markedly increased and usually there was a depression following morphine.

Summary

1. Eleven normal nonpregnant and four normal pregnant women and two patients with diabetes insipidus were given intravenous infusions of 5 per cent dextrose and their urinary outputs were measured for twenty-four hours. After several days, the procedure was repeated with the patient receiving morphine sulphate, ¼ grain (16 mg.), intramuscularly at the time the intravenous infusion was begun. The results obtained on the control day were compared with those obtained on the morphine day.

2. During the intravenous administration of 5 per cent dextrose at a constant rate over a five-hour period in normal subjects, there is an initial diuresis in the first two hours followed by a decrease in urinary output.

3. A single dose of morphine caused a suppression of urinary output which tended to eliminate the initial diuretic surge normally seen in the first two hours. This was a constant effect but varied in degree.

4. On morphine test days, as compared with control days, there was no increase of specific gravity or chloride concentration of the urine. Hematocrit determinations taken before the infusion and again eight hours later were unchanged during both control and morphine days.

5. Two patients, one pregnant, were given single injections of Pitressin. There was an increased concentration of urinary chlorides and an increase in total chlorides. One patient had suppression of urinary output and the other showed an output about equal to that on the control day.

6. Two patients with diabetes insipidus demonstrated suppression of urinary output when given morphine. In one instance the total chlorides were decreased and in the other they remained unchanged.

7. These observations suggest that the data from dog experiments, indicating that morphine causes a release of antidiuretic hormone from the neurohypophysis, cannot be accepted in explanation of the antidiuretic effect of morphine in normal women.

Appendix

The first patient (L. B., aged 26 years) had a history of diabetes insipidus for the past twelve years. She had been taking 1 c.c. Pitressin tannate in oil every one and one-half to two days since 1940. Thorough studies in 1940 and again on this admission revealed no other demonstrable abnormality.

The second patient (M. D., aged 62 years) had the diagnosis of diabetes insipidus made in 1941. She had been taking injections of 1 c.c. Pitressin tannate in oil every three to four days in order to control her symptoms.

In order to re-affirm the diagnosis of diabetes insipidus, the method of Carter and Robbins[8] was used. This consists of an initial oral hydration period followed by the insertion of an indwelling catheter and the collection of two subsequent fifteen-minute urine

specimens to serve as controls. Intravenous infusion of 2.5 per cent sodium chloride was then given at the rate of 0.25 c.c. per kg. per minute over a period of 45 minutes. Urine was collected for each fifteen-minute interval during the infusion, and for 30 to 60 minutes after its conclusion. Aqueous Pitressin, 0.1 unit, was given intravenously to the diabetes insipidus patients thirty minutes after cessation of the infusion.

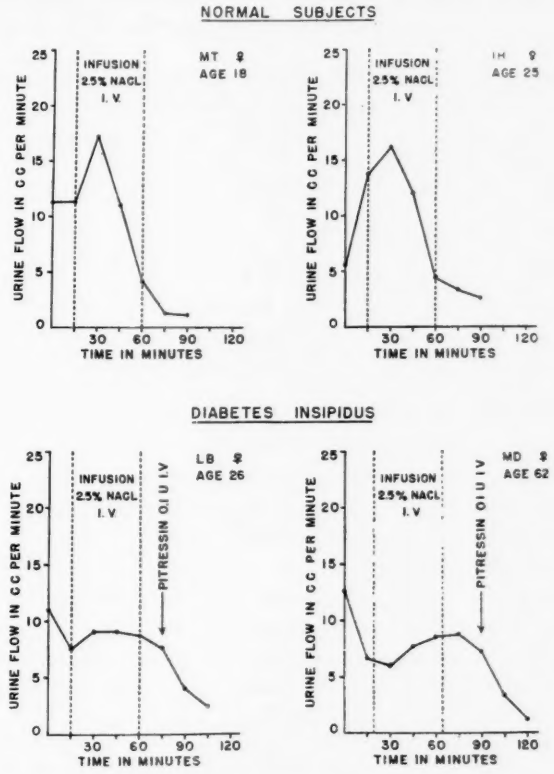

Fig. 7.—Graphic representation of the effect of intravenous hypertonic (2.5 per cent) sodium chloride solution on the urine output in normal women and in those with diabetes insipidus. This is the test of Carter and Robbins.[8]

Fig. 7 shows the results plotted in minute urine output. A typical diabetes insipidus curve was obtained on each of the test patients. This is characterized by the maintained or increased urine volume during the infusion of hypertonic saline, in contrast to the abrupt decrease in urine volume during the saline infusion in normal subjects (A. H. and M. T.). These control patients, aged 18 and 25 years, were on the gynecologic service awaiting sterilization.

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AN ELECTROPHORETIC STUDY OF MATERNAL, FETAL, AND INFANT SERA*

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MANY chemical and immunologic[1-9] and a few electrophoretic[10-14] comparisons have been made of sera from several species throughout the life span. Scarcely any data have been reported for embryonic sera.[4, 7, 15, 16] This paper reports studies on the changes in the electrophoretic patterns of maternal, fetal, and infant sera. The meaning of the patterns is discussed from the point of view of protein content, placental permeability, and species relationships. An attempt is made to correlate serum globulin content with the changes in antibody titer during the first few months of postnatal life.

Experimental

Blood was obtained from the umbilical cords of eight newborn infants (two were identical twins) and from their mothers soon after delivery. Blood was again taken by jugular vein from the same and other babies at various times during the first year. Samples of venous blood throughout the gestation period and at delivery were taken from mothers. Samples of blood were also taken from the hearts, up to the sixth month, of aborted or miscarried fetuses and from the umbilical cords of premature infants.

All of the analyses were made in a buffer 0.02 M with respect to sodium phosphate and 0.15 M with respect to sodium chloride (pH 7.4 and ionic strength 0.2).[17] The samples of sera were diluted with 2 parts of this buffer. Three ml. of each of these diluted sera were dialyzed in viscose casings against one liter of the buffer for twenty hours, whereupon the volumes were remeasured in order to correct for any change in volume during dialysis. The conductivity and pH of both the diluted sera and the dialysate were routinely taken. The conductivities were used in calculating the mobilities of the various electrophoretic components.

The analyses were carried out in a Tiselius apparatus[18] having a single-sectioned tall cell of 2 ml. capacity. The center section is 50 mm. tall, 15 mm. deep (along optic path) and each channel is 2 mm. wide. The channels are 10 mm. apart (center to center). Patterns obtained in this cell are indistinguishable after enlargement from those obtained in the standard 11 ml. Tiselius cell. A current of 18.7 Ma. flowed through the cell and produced a field strength of 6.5 volts/cm. All patterns were obtained by the scanning method of Longsworth,[19] on panchromatic plates (Kodak M) the light source being a 200-watt tungsten projector lamp. Pencil tracings of five times magnified patterns were measured with a planimeter. The components were segregated by drawing perpendiculars to the base line according to the procedure of Tiselius and Kabat.[17]

*The authors wish to acknowledge the valuable interest and assistance in obtaining fetal and infant sera rendered by Dr. P. A. di Sant'Agnese of Babies Hospital and Drs. John Field and J. M. Greer of the Department of Obstetrics and Gynecology.

Although most of the data on human serum found in the literature are given in grams per cent of protein calculated from nitrogen or density measurements, electrophoretic pattern areas were not converted into grams per 100 c.c. serum because the specific refraction increment* for each of the various electrophoretic components was not determined. The pattern area represents a composite of protein, lipid, and carbohydrate, all having different specific refractions and occurring in different concentrations in the various electrophoretic fractions.[20]

Reiss,[21] Robertson,[22] Arnd and Hafner,[23] Starlinger and Hartl,[24] and Adair and Robinson[25] have reported that the specific refraction varied from 0.0017 to 0.0023 or greater for the various serum fractions. Similar variations have been found for electrophoretically separated fractions.[26] The variations are less if the values are calculated from dry-weight measurements. Nevertheless, they are appreciable because of the diversity of the constituents of the fractions.

Beside the errors introduced by the complexity of the serum composition, there are systemic errors in the moving boundary method which influence the pattern area. The inequality in concentration of buffer ions in the serum and its dialysate at Donnon equilibrium[24] and the delta- and epsilon-effects[27] which are dependent on the nature of the buffer and the ratio of the colloid to the crystalloid ions[27, 28] give rise to boundary anomalies. These effects were reduced by diluting the samples with a buffer of high ionic strength.†

The delta- and epsilon-, especially the epsilon (descending) gradients are almost negligible in this phosphate-saline buffer. Analyses of sera or serum fractions containing no gamma-globulin or component of similar low mobility reveal epsilon-boundaries of extremely low areas, as is illustrated in Fig. 1. The rat serum pattern illustrated in Fig. 1*A* was taken from the top half of ultra-centrifuge tubes after prolonged centrifugation at 50,000 r.p.m. and is probably not entirely gamma-globulin-free. Normal chick (40 days old) serum (Fig. 1*B*) has no component of low mobility.

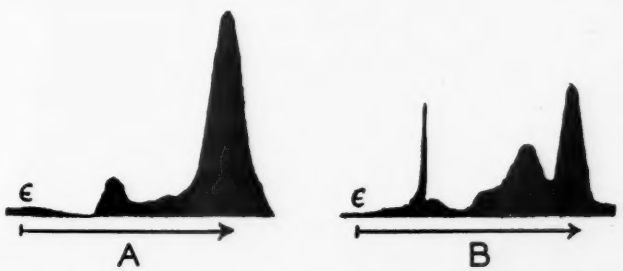

Fig. 1.—Electrophoresis patterns (from the descending limb) of γ-globulin-free rat serum (A) and chick serum (B) illustrating the low ϵ or salt boundary obtained in phosphate-saline buffer of ionic strength 0.2.

Some samples of sera were ether-extracted by the method of McFarlane.[29] Two volumes of serum were mixed thoroughly with one volume of ether and quickly frozen in a dry ice-alcohol bath. The sample was then allowed to thaw in the icebox for eight hours or longer, whereupon the serum layer was carefully removed from underneath the ether layer with a syringe and blunted needle. This process was repeated two additional times. McFarlane reports that this removes only part of the total lipids, but apparently does not denature the proteins.

*Species refraction increment is defined as the increase in the refractive index caused by the presence of 1 gm. of solute in 100 c.c. of solution.

†Phosphate-saline buffer mixtures of high ionic strength have been used routinely in this laboratory because (1) their boundary effects are small, (2) electrophoretically-separated samples may be assayed biologically or for nitrogen. (3) good patterns are obtainable on sera from all species so far examined, (4) all of their ions exist naturally in biological fluids, (5) when compared with the barbiturates it is relatively inexpensive.

Results

The data on maternal, fetal, and infant sera covering the gestation period and ten months of postnatal life in the infant are presented in Tables I, II, III, and IV and the results are summarized in the chart of Fig. 2. It may be

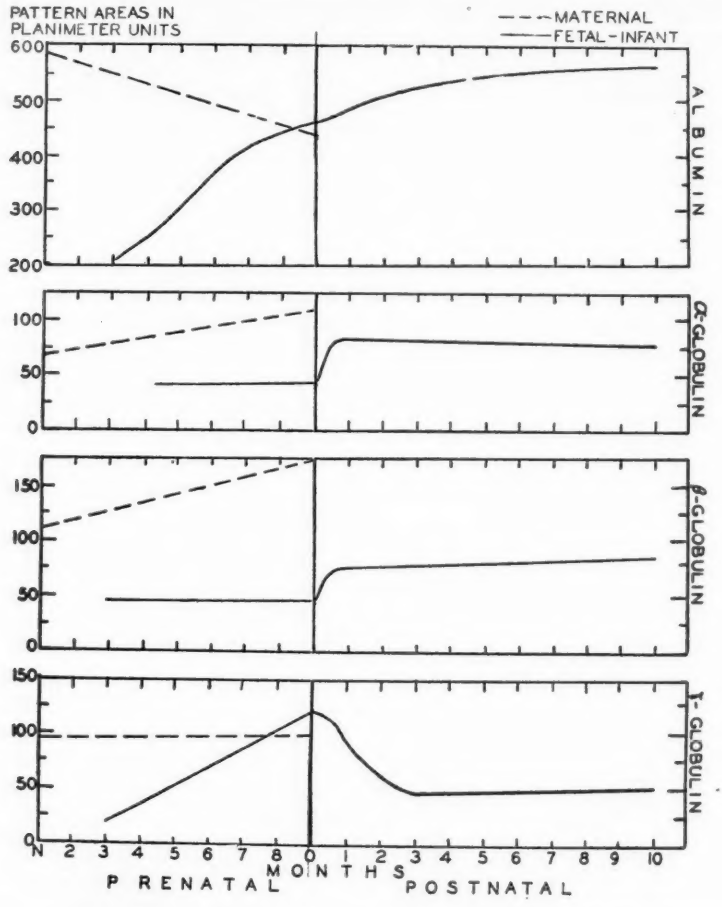

Fig. 2.—Chart indicating the development of serum proteins in the human fetus and during the first ten months of postnatal life. Changes in maternal serum during pregnancy are also shown.

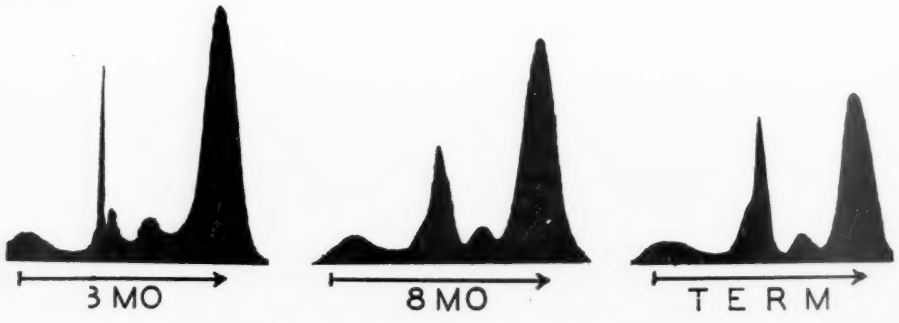

Fig. 3.—Pregnancy serum patterns.

observed (Table I, Figs. 2 and 3) that the albumin of the maternal sera decreases during pregnancy, whereas alpha- and beta-globulins, particularly beta-globulin, increase greatly and gamma-globulin remains essentially unchanged.

TABLE I. ELECTROPHORETIC DATA ON PREGNANT MOTHER'S SERUM

MONTH OF PREGNANCY	COMPOSITION									
	ARBITRARY UNITS					PER CENT				
	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	ALBUMIN GLOBULIN
2nd*	590	50	120	75	835	70.6	6.0	14.4	9.0	2.4
3rd*	515	60	100	75	750	68.7	8.0	13.3	10.0	2.2
4th*	520	80	125	75	800	65.0	10.0	15.6	9.4	1.9
5th*	500	75	145	75	795	62.8	9.5	18.2	9.5	1.7
6th*	505	90	155	85	835	60.5	10.8	18.5	10.2	1.5
7th	490	95	160	95	840	58.5	11.3	19.0	11.2	1.4
8th	460	105	170	95	830	55.3	12.7	20.6	11.4	1.3
9th	550	125	180	100	955	57.5	13.1	18.9	10.5	1.3

*From the same patient.

TABLE II. ELECTROPHORETIC FRACTIONATION OF MATERNAL SERA AT DELIVERY

IDENTIFICATION	COMPOSITION									
	ARBITRARY UNITS					PER CENT				
	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	ALBUMIN GLOBULIN
I	420	110	170	90	790	53.1	14.0	21.5	11.4	1.1
II	430	135	150	100	815	52.8	16.5	18.4	12.3	1.1
III	360	80	180	90	710	50.6	11.3	25.4	12.7	1.0
IV	420	85	140	70	715	58.9	11.9	19.6	9.8	1.4
V	375	110	90	80	655	57.2	16.8	13.8	12.2	1.3
VI	550	85	190	90	915	60.0	9.3	20.8	9.9	1.5
VII	455	90	155	190	890	51.1	10.1	17.4	21.4	1.0

TABLE III. ELECTROPHORETIC FRACTIONATION OF FETAL SERA.

AGE IN MONTHS	COMPOSITION									
	ARBITRARY UNITS					PER CENT				
	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	ALBUMIN GLOBULIN
3	190	20	35	15	260	73.1	7.7	13.4	5.8	2.72
4	230	20	35	30	315	73.0	6.4	11.1	9.5	2.71
5	425	40	45	50	560	75.9	7.2	8.0	8.9	3.15
6	405	30	35	85	555	73.0	5.4	6.3	15.3	2.70
7	425	45	60	90	620	68.5	7.3	9.7	14.5	2.18
9	450	30	45	160	685	65.6	4.4	6.6	23.4	1.91

Almost the opposite condition prevails in the developing embryo, as is illustrated in the chart of Fig. 2 and the patterns of Fig. 4. There is a marked rise in albumin and gamma-globulin but the alpha- and beta-globulins remain at the same low throughout the period investigated (from the third month to parturition). In the first few days of postnatal life, however, alpha- and beta-globulins

TABLE IV. ELECTROPHORETIC FRACTIONATION OF INFANT SERA

IDENTIFICATION	COMPOSITION: ARBITRARY UNITS: ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	COMPOSITION: PER CENT: ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	ALBUMIN GLOBULIN	METHOD OF FEEDING
Umbilical Cord											
I*	520	60	70	140	790	65.8	7.6	8.9	17.7	1.9	
II	470	40	60	95	665	70.6	6.1	9.1	14.2	2.4	
IIIA†	425	40	35	110	610	69.6	6.6	5.8	18.0	2.4	
IIIB†	435	40	35	100	610	71.3	6.6	5.7	16.4	2.5	
IV	445	45	25	110	625	71.1	7.2	4.0	17.7	2.5	
V	425	40	35	95	595	71.5	6.7	5.9	15.9	2.5	
VI	555	45	40	100	730	76.0	4.8	5.5	13.7	3.2	
VII	450	30	45	160	685	65.7	4.4	6.5	23.4	1.9	
Five Days Old											
II	515	80	60	100	755	68.2	10.6	7.9	13.4	2.1	
IIIA	380	50	35	110	575	66.1	8.7	6.1	19.1	2.0	
IV	450	60	55	110	675	66.6	8.9	8.1	16.4	2.0	
V	445	50	80	110	685	65.0	7.3	11.7	16.0	1.9	
Ten Days Old											
VIII	465	55	65	110	695	67.0	7.9	9.3	15.8	2.0	Breast
IX	430	80	90	120	720	59.7	11.1	12.5	16.7	1.5	Formula
Fifteen Days Old											
VI	360	75	50	40	525	68.6	14.3	9.5	7.6	2.2	Breast
One Month Old											
VI	530	80	30	210	850	62.3	9.4	3.6	24.7	1.7	Breast
X	460	60	100	40	660	69.6	9.1	15.2	6.1	2.3	Breast
XI	555	85	70	85	795	69.8	10.7	8.8	10.7	2.3	–
Two Months Old											
VI	560	80	90	55	785	71.4	10.2	11.4	7.0	2.5	Breast
XII	450	80	80	80	690	65.2	11.6	11.6	11.6	1.9	–
XIII	400	50	40	45	535	74.8	9.3	7.5	8.4	3.0	–
Three Months Old											
VI	470	75	80	50	675	69.7	11.1	11.8	7.4	2.3	Breast
XIV	490	95	70	45	700	70.0	13.6	10.6	6.4	2.5	Formula
XV	520	75	50	35	680	76.5	11.0	7.3	5.2	3.2	Formula
XVI	575	70	100	45	790	72.8	8.8	12.7	5.7	2.7	Formula
Six Months Old											
XIV	440	75	80	30	625	70.3	12.1	12.8	4.8	2.4	Formula
XVII	655	100	110	50	915	71.6	10.9	12.0	5.5	2.5	–
XVIII	515	75	65	65	720	71.6	10.4	9.0	9.0	2.5	–
Ten Months Old											
XIX	500	45	55	60	660	75.8	6.8	8.3	9.1	3.1	–
XX	465	60	75	45	645	72.1	9.3	11.6	7.0	2.7	–
XXI	550	65	90	45	750	73.3	8.7	12.0	6.0	2.8	–

*Data for corresponding mothers recorded in Table II.
†Twins.

TABLE V. IMMUNIZATION DATA

ANTIGEN	INFANTS IMMUNIZED: AT BIRTH	AT 3RD, 4TH, AND 5TH MONTHS
Pertussis	XI, XII, XIII, XIV.	XIV, XVII, XVIII.
Diphtheria	XI, XII, XIII, XIV.	XIV, XVII, XVIII.
Tetanus	XI, XII, XIII, XIV.	XIV, XVII, XVIII.
Pneumococcus polysaccharide	XI, XII, XIII.	

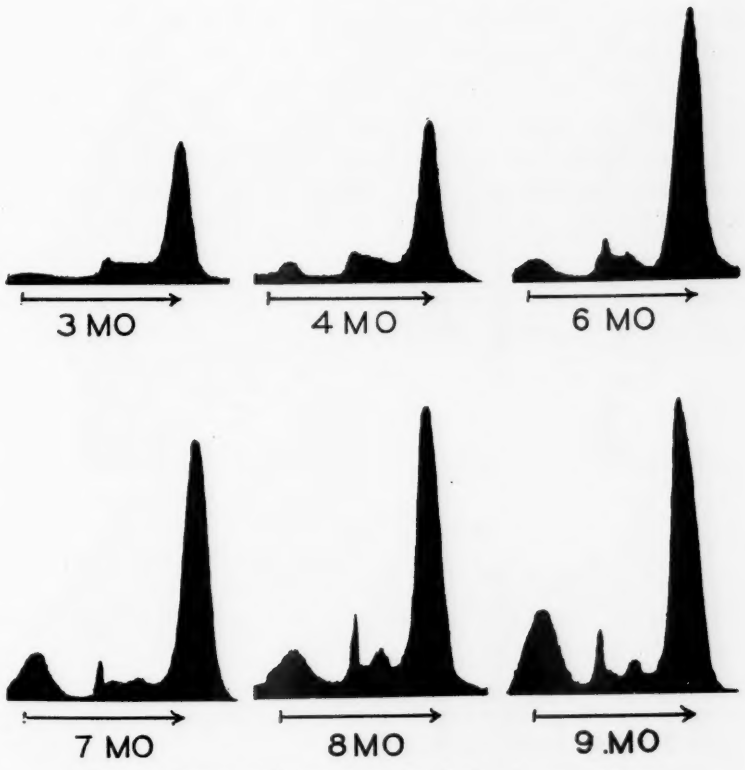

Fig. 4.—Serum patterns from developing human fetuses.

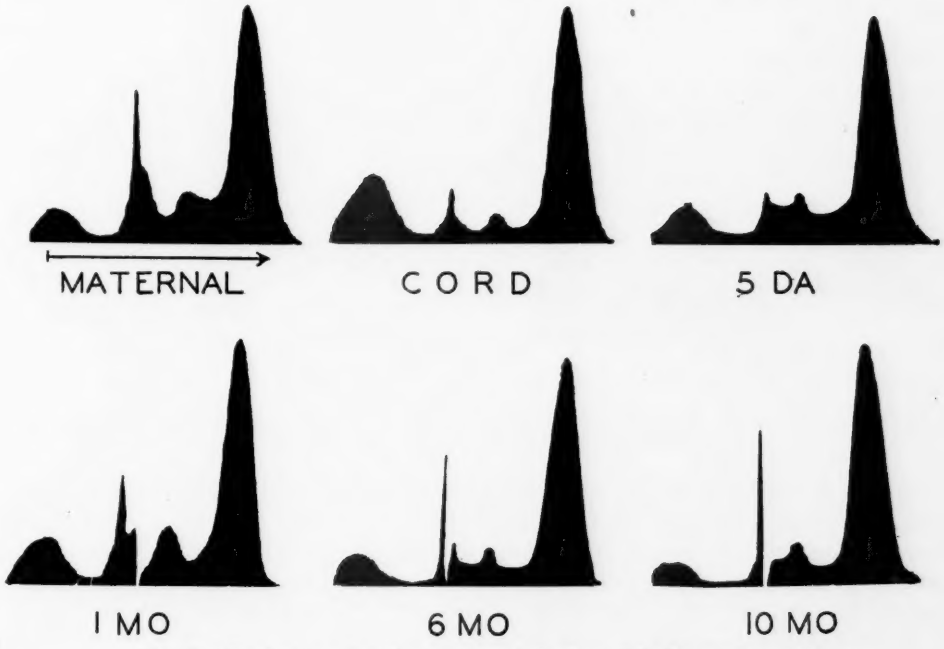

Fig. 5.—Typical maternal, newborn infant, and baby serum patterns.

increase rapidly, albumin slightly, and gamma-globulin begins to decrease. The ratio of albumin to globulin drops from 2.5 to 2.0 during the first five days, due to the rapid rise of alpha- and beta-globulins, then rises again during the next 3 weeks as a result of the marked decrease in gamma-globulin. Between the first and tenth month the albumin/globulin ratio rises again to a value of 2.7 to 3.1 as a result of the persistent low level of gamma-globulin and the substantial increase in albumin. Typical patterns of infant sera during the first year are illustrated in Fig. 5.

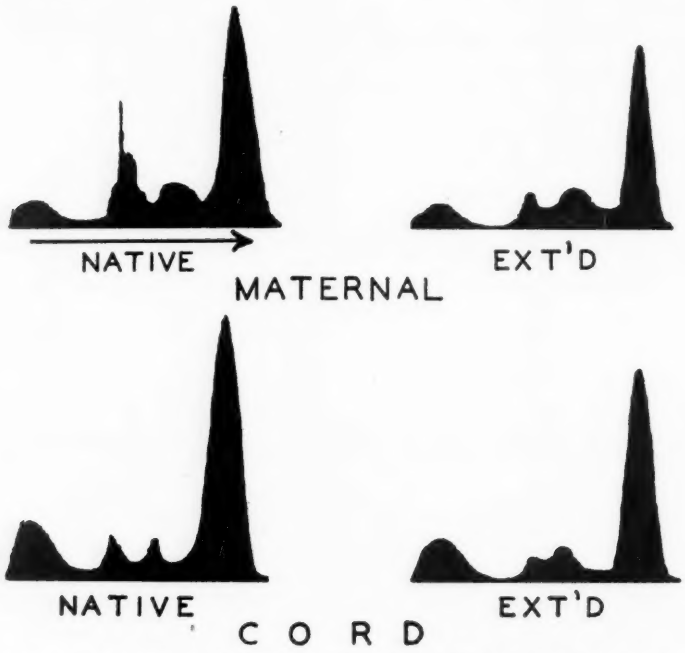

Fig. 6.—Maternal and newborn infant serum patterns before and after ether extraction.

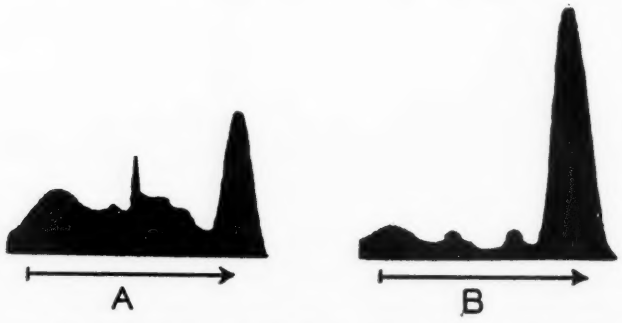

Fig. 7.—Macaque mulatto monkey serum patterns; (A) maternal at parturition, hypophysectomized 35 days prepartum, (B) newborn.

The wide fluctuations in the serum pattern of infant number VI (the daughter of one of the authors) should be noted. At birth, the pattern coincided with the average except that the albumin was slightly high. At 15 days, the total pattern area had decreased by about 30 per cent, and at one month it had more than regained its loss with an enormous increase in gamma-globulin. By the second and third months the gamma-globulin had diminished to about one-fourth the high value. No illness was noticed in the child during this period. Immunologic data are given in Table V.

TABLE VI. ELECTROPHORETIC DATA ON SERA BEFORE AND AFTER ETHER EXTRACTION

IDENTIFICATION	COMPOSITION (ARBITRARY UNITS)					CHANGE (PER CENT)					NITROGEN MG/C.C.
	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	
Native	420	110	170	90	790						
Maternal						−28.6	0	−58.8	0	−27.8	
Ext'd	300	110	70	90	570						
Native	530	60	70	140	790						
Cord						−24.5	0	−21.4	−7.1	−18.3	
Ext'd	400	60	55	130	645						
Native	500	90	150	90	830						2.94
Pregnancy*						−15.0	0	−46.6	−27.6	−20.5	
Ext'd	425	90	80	65	660						2.61
Native	530	90	110	110	840						
Normal						0	−22.2	−50.0	−9.1	−10.1	
Ext'd	530	70	55	100	755						
Native	740	75	170	180	1165						3.12
Lipemic†						−24.3	0	−47.0	−27.8	−26.7	
Ext'd	560	75	90	130	855						3.23

*Sixth month.
†Apparently normal male medical student.

Data obtained before and after ether extraction for pregnancy, maternal, umbilical cord, normal, and lipemic sera are reproduced in Table VI. Electrophoretic pattern areas were compared with nitrogen contents (Kjeldahl method) before and after ether extraction in two of the cases. Both electrophoretic and nitrogen analyses were made on aliquots of the same diluted and dialyzed material. Patterns of maternal and cord sera are shown in Fig. 6.

In order to demonstrate the wide divergence which may occur in the sera of mother and fetus, a comparison is made in Fig. 7 of serum from a macaque mulatto monkey hypophysectomized 35 days before delivery and from her newborn offspring.*

Discussion

The foregoing data indicate that the total electrophoretic pattern area for the newborn infant sera is smaller than that for the mothers'. The small amount of alpha- and beta-globulin in the infant sera is responsible for this difference because both the albumin and gamma-globulin areas are greater in the latter. This is in agreement with the findings of Longsworth, Curtis and Pembroke,[13] whose illustrated patterns, however, did not appear to agree (probably due to the large delta-boundary in the maternal plasma pattern) with any of their own plasma data.

The changes which occur in pregnancy serum are in agreement with the observations of Lagercrantz[14] who studied many more cases than are presented here.

Ether extraction resulted in a much greater diminution in the pattern areas of the maternal and cord sera than in the normal nonpregnant serum. A large proportion of the material extractable from the maternal and cord sera had been associated with the albumin fraction as well as with the beta-globulin, whereas

*Supplied by Dr. P. E. Smith.

extraction of the normal nonpregnant reduced essentially only the apparent beta-globulin. That this extraction procedure[29] removes material of low nitrogen content is evidenced by the fact that the ratio of pattern area to nitrogen was reduced upon ether extraction (see Table VI). This is in agreement with the findings of Zeldis et al.,[30] who extracted lipids from human and dog sera by an ether-alcohol method described by Blix.[31] This extraction procedure is more laborious, involving precipitation of the protein. It removes more lipids than the method of McFarlane.[29] Such studies offer a better understanding of the changes which take place in various blood sera.

The serum gamma-globulin level during the first few months of infancy is of especial interest. Many investigators[5, 32, 33] and others have demonstrated the presence of antibodies in newborn infant sera. Antibodies are, no doubt, a part of the gamma-globulin but in most cases[34] have little quantitative relation to it, as is again demonstrated here by the fact that gamma-globulin in cord sera is consistently higher than that of the maternal, whereas antibody titers are never higher.[5, 32, 33] Moreover, there was no difference in the gamma-globulin level of sera from babies immunized with pneumococcus polysaccharide, pertussis, tetanus, and diphtheria and those unimmunized (see Tables IV and V).

If serum proteins cross from maternal to fetal blood, the placenta must play an active role in selecting the serum component transferred, since the levels of gamma-globulin and albumin are higher and those of alpha- and beta-globulin are lower in the fetal blood at birth. It has been shown by Pedersen,[35] however, that in human sera alpha-globulin contains the molecules having a sedimentation constant of 20 Svedberg units (molecular weight about one million), and that beta-globulin contains the large lipoprotein complexes. Neither of these large molecules would be expected to cross the placental wall as readily as the smaller albumin (mol. wt. 70,000) and gamma-globulin (mol. wt. 160,000) molecules. Nevertheless, the placenta and fetus are doubtless able to regenerate or synthesize their own blood proteins because the fetal serum pattern is little influenced by large variations found in maternal sera, particularly in toxemia[14] and in the example of the hypophysectomized monkey (Fig. 6), and also because the fetus synthesizes its own proteins after birth.

Evidence for the placental transfer or placental synthesis of gamma-globulin is offered by the data of Tables II and IV (see gamma-globulin curve, Fig. 2). The decrease in gamma-globulin during the first month of postnatal life corresponds to the antibody disappearance rate one would expect from the findings of Schoenheimer et al.[36] They found that in the rabbit the half-life of an antibody molecule was about fourteen days. Assuming the same decay rate for the rest of gamma-globulin as for the antibodies and some postnatal replenishment, it would therefore be expected to decrease according to the curve of Fig. 2. It may be pointed out here that the flocculation of infant serum with Hayem's solution, calcium chloride, and many antigens decreases according to the gamma-globulin curve of Fig. 2.[32, 33, 37, and others] Further evidence for placental transfer or synthesis of globulin is offered by Pommerenke,[38]

who found that the venous blood of the umbilical cord contained significantly more globulin (by salt fractionation) than the arterial blood.

A rise in euglobulin after ingestion of colostrom has been reported by Lewis and Wells.[39] This increase was undoubtedly due to an increase in beta-globulin and perhaps also in alpha-globulin, as our results on 5- and 10-day-old infants show (see Fig. 5). Although colostrum contains antibodies,[32, 39] its ingestion does not increase the antibody titer[40, 41] or the quantity of gamma-globulin in man. Ratner, Jackson and Gruehl[42] have arrived at the same conclusion from their studies on guinea pigs. On the other hand, Jameson, Alvarez-Tostado and Sorter,[10] San Clemente and Huddleson,[11] Polson,[12] and Charlwood and Thomson[43] have observed that the ingestion of colostrum by newborn calves, foals and lambs caused a rapid increase in gamma-globulin which, unlike newborn infants, was almost absent at birth. Moreover, it has been shown that the gamma-globulin level remains low throughout the fetal development of pigs.[15] It would appear, therefore, that the protein pattern of fetal serum depends on the type of placenta concerned and that the gamma-globulin and the antibody titer are higher at birth and decrease thereafter in human serum, whereas they are lower and increase with the ingestion of colostrum in the lower species examined.

Summary

Serum albumin and gamma-globulin increase rapidly during the development of the human fetus, whereas the alpha- and beta-globulins remain at a low level. The alpha- and beta- globulins rise appreciably and albumin decreases in maternal sera during pregnancy. The high gamma-globulin in newborn infants decreases markedly during the first month or two of life, whereas all of the other serum components rise. The view that the ingestion of colostrum maintains or raises the antibody level of infants is not supported by our findings.

The serum patterns are discussed from the viewpoint of lipid content, placental permeability, and species differences.

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THE RELATION OF RH INCOMPATIBILITY TO ABORTION

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IN 1928, Hirszfeld[1] observed that there seemed to be a higher than random occurrence of incompatible ABO matings among women with histories of two or more abortions. Influenced by that observation, Levine,[2, 3] early in the course of his studies on the relation of the Rh blood factors to erythroblastosis fetalis, suggested that perhaps Rh incompatibility between mother and fetus might give rise to abortions and miscarriages, as well as to stillbirths. In a later paper,[4] he recorded the high rate of ten abortions or miscarriages in 37 pregnancies of seven patients. It is not clear, however, from the report, whether this rate of 27 per cent abortion was in a group made up wholly of Rh-negative women or not; nor was the distribution of abortions among the mothers given. Later in 1943, Schwartz and Levine[5] examined nine cases of mothers who had had two or more early abortions in succession. Eight of these nine women turned out to be Rh positive, and these workers then concluded, on this rather slight basis, that while Rh incompatibility may well produce late abortions, i.e., in the second trimester of pregnancy, it is quite unimportant in bringing about early abortions. Yet against any such positive conclusion as to the role of Rh incompatibility even in late abortion were their own data, which showed that of 11 premature births, only one involved an Rh-negative mother.

Beside these observations and conjectures one must place the findings of Bornstein and Israel[6] of definite Rh antigen in a 17 cm., 4-month-old unmacerated fetus, and the finding by Kemp[7] of B antigen in a 37-day-old fetus. Although so early a development of antigens would render early maternal isoimmunization at least possible, it was reported, on the other hand, by Page, Hunt, and Lucia[8] that ten weeks of antibody production are required to produce appreciable fetal damage. The sum of four months and ten weeks would render dubious any likelihood of Rh incompatibility leading to abortion prior to the twenty-eighth week of pregnancy, the term customarily chosen for delimiting miscarriage and abortion, on the one hand, from premature birth on the other.

The question raised was not greatly clarified by the further data reported by Potter, Davidsohn, and Crunden,[9] and by Hunt.[10] These investigations merely ascertained the frequency of Rh-negative women among women who aborted under observation or were known to have histories of habitual abortion. In the first of these two studies, 40 of 45 women who aborted were Rh positive, 5 of 45 were Rh negative. But this finding that abortions may occur in Rh-positive women as well as Rh-negative women is hardly surprising; and the 11 per cent frequency of the Rh-negative women in this group, where about 15 per cent is to be expected, has a standard error of ± 4.7 per cent. No conclusion is possible, therefore, as to whether the abortion rate in Rh-negative women is

really higher or lower than in Rh-positive women. In Hunt's study, 22 of 25 women who aborted habitually were found to be Rh positive. But once again, the finding, which exactly matches the expectation of 85 per cent Rh positive to 15 per cent Rh negative, has no bearing on the question whether Rh-negative women have a higher abortion rate subsequent to sensitization or not. For "habitual abortion" may very well be caused by factors other than Rh incompatibility without affecting the possibility of a raised abortion rate due to the latter. In a continuation of this study, Hunt[11] added 93 cases of recurrent abortion culled from approximately 75,000 women admitted to the Mayo Clinic. Among these 93, the percentage of Rh-negative women was 18.3 per cent. In 34 cases of true habitual abortion, there were seven Rh-negative women, or 20.6 per cent. These values are somewhat higher than the expected 15 per cent of Rh-negative women in the general population, but two of these Rh-negative women had Rh-negative husbands, a fact which rules out Rh incompatibility as the cause of their habitual abortion. The standard error of the first percentage of Rh-negative women is ± 4.0 per cent, and that of the second is even larger, so that no statistical significance can be attached to their differences from the expected 15 per cent.

For an adequate analysis, it would seem essential to distinguish and to determine separately the abortion rates for Rh-negative women before and after they have become sensitized. The nearest approach to this has been the separate classification of women who have had at least one infant with hemolytic disease. Race, Taylor, Cappell, and McFarlane[12] did this for 178 pregnancies of 44 women, and found 8 abortions in 108 pregnancies (7.4 per cent) prior to the delivery of an erythroblastotic infant, and three abortions in 26 pregnancies (11.5 per cent) after the delivery of an erythroblastotic infant. These are both unusually low abortion rates, as compared with those found in the large groups studied by Tietze[13] and in the present investigation, and the small number of pregnancies in the posterythroblastotic group in particular renders that finding of no statistical significance. The study is interesting, however, as being the first to define the problem clearly. Hunt[11] also cites the histories of 13 patients who delivered erythroblastotic infants, but with only seven subsequent pregnancies, the occurrence of no abortions is not indicative of anything. In 122 Rh-negative women, each one of whom had at least one erythroblastotic infant, as reported by Potter,[14] there were 51 abortions in 248 pregnancies (20.6 per cent) prior to the birth of an infant with the disease, and 17 abortions in 107 pregnancies (16.0 per cent) following the the birth of such an infant. (Many of these abortions were known to have been induced.) These results are suggestive; but the difference of 4.6 per cent is again without statistical significance. For all these studies, it should be pointed out that it is probably not valid to take the birth of an infant with hemolytic disease as equivalent to sensitization. In the Baltimore Rh Typing Laboratory, erythroblastosis has occurred in the offspring of only 53, or 67.0 per cent, of 79 isoimmunized women[15]; and a milder, incipient degree of immunization, too weak to produce clinical symptoms of erythroblastosis, might conceivably produce early miscarriage.

The latest study on this subject, by Overstreet, Traut, Hunt, and Lucia,[16] although it is considerably more extensive than any of those previously discussed, has again estimated the abortion rate for all Rh-negative women, irrespective of their immunization. The use of the first five lunar months, instead of the first seven, to define the period of miscarriage and abortion, renders these data rather less comparable with those of other studies, including the present one. One thousand thirty-eight pregnancies of 226 Rh-negative women were compared with 1,129 pregnancies of 237 Rh-positive women. No exclusion was made of Rh-negative women who had Rh-negative husbands, nor was there any

separation of Rh-negative sensitized from nonsensitized women. The total abortion rate found was 15.2 per cent for Rh positive, 12.4 per cent for Rh negative, the difference being attributed to sampling error. A definite rise in abortion in multigravidas, as compared with primigravidas, was found in both groups: Rh positive, from 12.2 per cent to 17.8 per cent; Rh negative, from 10.9 per cent to 13.9 per cent. It was not recognized, however, that the higher average number of pregnancies in the Rh-positive group would quite account for the difference between the Rh-positive and Rh-negative groups in the abortion rate.

Forty-five mothers who had borne an erythroblastotic child were given separate consideration. The abortion rate for all pregnancies of these women was 14.1 per cent, with a rise from 6.7 per cent in the first pregnancy to 17.8 per cent in multigravid pregnancies. The differences between these values and those for the Rh-positive control group are, however, not significant. The authors, while not claiming to have disproved that a relation between Rh incompatibility and abortion may exist, yet concluded that, since the Rh antigen probably does not develop in the first two to four weeks of pregnancy, and since about ten weeks thereafter are required for sensitization to reach a level sufficient to do appreciable fetal damage, there can be little chance of this occurring before twenty weeks, the onset of the viable period.

Hunt[11] has added a study of 228 Rh-positive and 228 Rh-negative women, with 36 abortions and miscarriages in 377 pregnancies (9.5 per cent) in the former, and 48 in 333 (14.4 per cent) in the latter. The difference is not statistically significant, and is in the opposite direction to that found in the larger group studied by Overstreet and associates.[16]

One may summarize all the studies reviewed above by saying that in a statistical sense they have failed either to establish or to disprove the existence of a relation between Rh isoimmunization and abortion. A final answer to this question can be given only by comparing an adequate sample of the histories of Rh-negative women, dating from the onset of sensitization in each case, with those of a carefully matched control group.

Present Study

In previous discussions of the possible relation of Rh incompatibility to miscarriage and abortion, the question does not appear ever to have been clearly posed. For statistical assurance, it is necessary to put it in the following terms: Is there any significant difference between the frequency of abortion and miscarriage in Rh-negative women, known to be actually sensitized, and for those particular pregnancies in which the fetus is Rh positive, and the frequency of abortion and miscarriage in other women?

When the problem is framed in these terms, it becomes clear that studies of the total frequency of abortion and miscarriage in all Rh-negative women, as compared with Rh-positive women, serve to obscure rather than to clarify the issue. In the first place, fetuses that are Rh negative themselves, in an Rh-negative mother, would not be expected to abort by reason of Rh incompatibility, irrespective of whether or not the mother is sensitized. Such cases represent 27.7 per cent of the pregnancies of Rh-negative women married to Rh-positive men (Rh-positive heterozygotes = 55.4 per cent of all Rh-positive individuals, and one-half of the children of such unions would be Rh negative). Since about 28 per cent of the pregnancies of Rh-negative sensitized women are therefore not

TABLE I. ABORTIONS PER PREGNANCY IN THE TOTAL WHITE POPULATION STUDIED

	ORDINARY PREGNANCY											
GRAVIDA	1ST	2ND	3RD	4TH	5TH	6TH	7TH	8TH	9TH	10TH PLUS	TOTAL	PER CENT
i	197/1684										197/1684	11.70 ± 0.78
ii	118/851	157/831									275/1662	16.55 ± 0.91
iii	58/362	64/362	84/362								206/1086	18.97 ± 1.19
iv	16/118	20/118	20/118	20/118							76/472	16.10 ± 1.7
v	12/79	13/79	11/79	9/79	18/79						63/395	15.95 ± 1.8
vi	3/37	4/37	5/37	6/37	9/37	6/37					33/222	14.86 ± 2.4
vii	7/34	3/34	6/34	5/34	7/34	2/34	5/34				35/238	14.71 ± 2.3
viii	1/11	0/11	4/11	1/11	3/11	5/11	2/11	3/11			19/88	21.59 ± 4.4
ix	0/6	0/6	0/6	0/6	0/6	0/6	1/6	0/6	0/6		1/54	18.52 ± 5.3
x+	1/9	1/9	0/9	1/9	1/9	2/9	1/9	5/9	2/9	8/21	22/102	21.57 ± 4.1
Total	413/3171	262/1487	130/656	42/294	38/176	15/97	9/60	8/26	2/15	8/21	927/6003	
Per cent	13.02 ± .60	17.62 ± .99	19.82 ± 1.56	14.29 ± 2.0	21.6 ± 3.1	15.5 ± 3.7	15.0 ± 4.6	30.8 ± 9.1	13.3 ± 8.8	38.1 ± 10.6		15.44 ± 0.47

Diagonal line separates:

Prior half histories: 14.7 ± 0.76 per cent Latter half histories: 19.1 ± 0.85 per cent

pertinent to the point at issue, a considerable number of such pregnancies must be studied to render any but a large differential statistically significant. In other words, unless very large numbers of cases are studied, the absence of any apparent difference in abortion frequency between Rh-negative sensitized women and their controls is likely to be due to the inclusion of Rh-negative offspring among the offspring of the Rh-negative sensitized women, rather than to the absence of any real difference. On the other hand, any differential that can be found and established statistically is really far larger than would appear at first sight, unless this bias has been allowed for.

Division of the individual subjects into three groups, the Rh positive, the Rh negative nonsensitized, and the Rh negative sensitized, is no less important to a clear analysis. The first two classes can be readily and accurately determined on the basis of tests during the current pregnancy, but without a complete history of tests made during each past pregnancy from the first on, the classification of the third group entails an unavoidable bias. Only for women in their first pregnancy, or for a certain few in their second, could it be positively determined, in the present study, at which pregnancy the sensitized condition had arisen. Consequently, in classifying women as sensitized solely on a current basis, an undeterminable number of pregnancies were classed as sensitized when they ought really to have been classed as nonsensitized. The two-year survey of the Baltimore Rh Laboratory reports the initial occurrence of isoimmunization in 228 multigravidas as 45.6 per cent in the second pregnancy, 21.5 per cent in the third, 13.6 per cent in the fourth, 4.8 per cent in the fifth, 8.3 per cent in the sixth, etc. Thus 54.4 per cent of the women eventually sensitized were not yet sensitized in their second pregnancy, 32.9 per cent in their third, and 19.3 per cent in their fourth. It can therefore be estimated that nearly all first pregnancies of women eventually sensitized were nonsensitized, as well as about one-half of the second pregnancies, about one-third of the third pregnancies, and about one-fifth of the fourth pregnancies. Consequently, any observed difference in the frequency of spontaneous abortion between women classified into "sensitized" and "nonsensitized" on the basis of their condition in current pregnancies should be increased by corresponding fractions. This consideration makes it clear that if a real difference in frequency of abortion should exist, it would, in a study such as the present, where the actual incidence of the sensitized state is not known for most of the subjects, be necessary to tabulate the frequencies of abortions by ordinal pregnancies. No difference can be expected to emerge until at least the third pregnancy is reached.

The frequencies of abortion are known[13] also to increase with increasing family size, at least in certain social and economic categories of the population. It was accordingly decided to tabulate the abortions also according to the gravidity of the women. The result of the dual tabulation was a triangular table, such as that presented for the total white population in Table I. This table reveals an abortion frequency of 15.44 per cent in the 6,003 pregnancies of the 3,171 white women included in the study.

The data used in the investigation consisted of the obstetric histories taken by regular workers at the Baltimore Rh Laboratory. Each woman was asked to give the date and outcome of every one of her pregnancies. Termination of any pregnancy prior to the twenty-eighth week from the last menstruation was regarded as an abortion (or miscarriage). Only in a few instances was information given as to whether the abortion was spontaneous or not. All abortions, including those induced, were therefore included in the data, inasmuch as no reliable criteria for separating spontaneous from induced abortions appeared to exist. Although this fact may be taken to mean that the "real" frequencies

TABLE II. INCIDENCE OF ABORTION IN TWO INDEPENDENT SAMPLES OF 1,250 RH-POSITIVE WOMEN (MATCHED FOR GRAVIDITY i, ii, iii, AND iv OR MORE)

	ORDINAL PREGNANCY						
	1ST	2ND	3RD	4TH	5TH	6TH	7TH PLUS
	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.
Sample 1	158/1250	161/919	110/589	43/292	28/159	13/90	32/133
Sample 2	158/1250	154/919	119/589	51/292	29/146	12/78	14/78
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Sample 1	12.63	17.5	18.7	14.7	17.6	14.45	24.02
Sample 2	12.63	16.76	20.2	17.46	19.85	15.38	17.95

TABLE III. FREQUENCY OF ABORTION IN RH-POSITIVE, RH-NEGATIVE NONSENSITIZED, AND RH-NEGATIVE SENSITIZED WOMEN

	ORDINAL PREGNANCY						
	1ST	2ND	3RD	4TH	5TH	6TH	7TH PLUS
	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.
Rh+	291/2500	193/1252	101/626	37/323	33/212	16/112	30/143
Rh– nonsens.	134/1155	86/546	41/260	19/133	12/80	2/39	3/44
Rh– sens.	25/209	18/142	17/89	7/52	11/35	3/22	8/34
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Rh+	11.64 ± 0.64	15.42 ± 1.02	15.97 ± 1.46	11.5 ± 1.8	15.6 ± 2.5	14.3 ± 3.3	21.0 ± 3.4
Rh– nonsens.	11.6 ± 0.94	15.7 ± 1.56	15.75 ± 2.26	14.3 ± 1.9	15.0 ± 4.0	6.9 ± 4.1	6.8 ± 3.8
Rh– sens.	11.95 ± 2.24	12.68 ± 2.8	19.1 ± 4.2	13.44 ± 4.3	31.4 ± 7.85	13.6 ± 7.4	23.5 ± 7.4

of spontaneous abortion are quite different from those reported, such a conclusion by no means invalidates the study. The subjects' histories were taken prior to their being typed for Rh. Untruthfulness and forgetfulness, as well as ignorance regarding very early miscarriage, may be assumed to have operated equally in the three groups of Rh-positive, Rh-negative sensitized, and Rh-negative nonsensitized women. The statistical reliability of the information was further checked by drawing two independent samples, of 1,250 women each, matched for gravidity, from the Rh-positive group. This comparison is set forth in Table II. None of the differences between corresponding classes of the two samples in Table II is statistically significant. In fact, in only one case, that of the 7 plus class, does the difference so much as equal twice the standard error of the mean of the two samples. In most cases the difference is less than the standard error.

The frequency of the Rh-negative type in Negroes is well known to be considerably below that in whites (slightly over one-half, in American Negroes). Therefore, in order to make the Rh-positive and Rh-negative groups comparable, it was necessary to match the proportion of Negroes in the Rh-positive samples against that in the two-Rh-negative groups. The frequency of Negroes in both Rh-negative groups (sensitized and nonsensitized combined) was taken as a basis for the quota of Negroes to be included in the Rh-positive group, and Negro individuals of equal gravidity were selected at random from the files to match those in the (combined) Rh-negative group. The number of women of other nonwhite ethnic groups was so small that they were all excluded from the study.

One other precaution was taken in order to make the three groups comparable. Each Rh-negative woman is followed up in the laboratory throughout the course of her current pregnancy and through delivery. This is not true of the Rh-positive women. It was early discovered that certain factors reduce the frequency of abortions reported for current pregnancies, in general. It was therefore necessary to exclude all data from the current pregnancy of each woman, and to rely upon records of past pregnancies alone. This unfortunately reduced the total number of pregnancies for the two Rh-negative groups, and so diminished the statistical information derivable from the full data; but it seemed necessary in order to make the three groups strictly comparable.

Comparison of the Three Groups

The ratio of total reported abortions and miscarriages to pregnancies was 701/5,168, or 13.56 per cent, for the 2,500 Rh-positive women; 297/2,247, or 13.2 per cent for the 1,155 Rh-negative nonsensitized women; and 89/583, or 15.25 per cent, for the 209 sensitized women. The total Rh-negative group, with 386/2,830 abortions, or 13.62 per cent, is obviously not different from the Rh-positive group. The difference between the Rh-positive and the Rh-negative sensitized women is also without significance ($\chi^2 = 1.3$; $P = 0.30$–0.20). It should be noted that the Rh-negative nonsensitized group has a smaller average number of pregnancies per woman (1.945), and the Rh-negative sensitized group a higher one (2.790), than the Rh-positive group (2.067). This must be due to an increasing probability that a Rh-negative woman will become sensitized as she has additional pregnancies, a factor that brings about a regular shift of individuals from the Rh-negative nonsensitized group to the sensitized group;* for when the two Rh-negative groups are combined, the average number of pregnancies (2.001) is very close to that of the Rh-positive group, as is to be expected, since the latter was indeed selected to correspond to the total Rh-negative group in gravidity frequencies. One may conclude, therefore, that

*That is to say, for example, the data for the fifth pregnancy are more largely contributed by v-gravida women for the Rh-negative nonsensitized group, but predominantly by women of higher gravidity for the Rh-negative sensitized group.

Rh-negative sensitized women actually have a slightly higher abortion frequency than Rh-positive women; but this is due to nothing more than their higher average order of pregnancies. This is in harmony with the already known fact that abortion frequency tends to increase with increasing gravidity.

Table III and Fig. 1 present the comparison of abortion frequency, by ordinal pregnancies, for the three groups of women. It should be kept in mind that as the number of pregnancies progressively drops in the higher classes, the statistical error consequently increases in inverse ratio. This is especially true of the Rh-negative sensitized group, a small sample to start with. For example, whereas the standard error of the rate for the first pregnancy of the Rh-positive group is only ± 0.64 per cent, for the sixth pregnancy of the Rh-negative sensitized group it is ± 7.4 per cent.

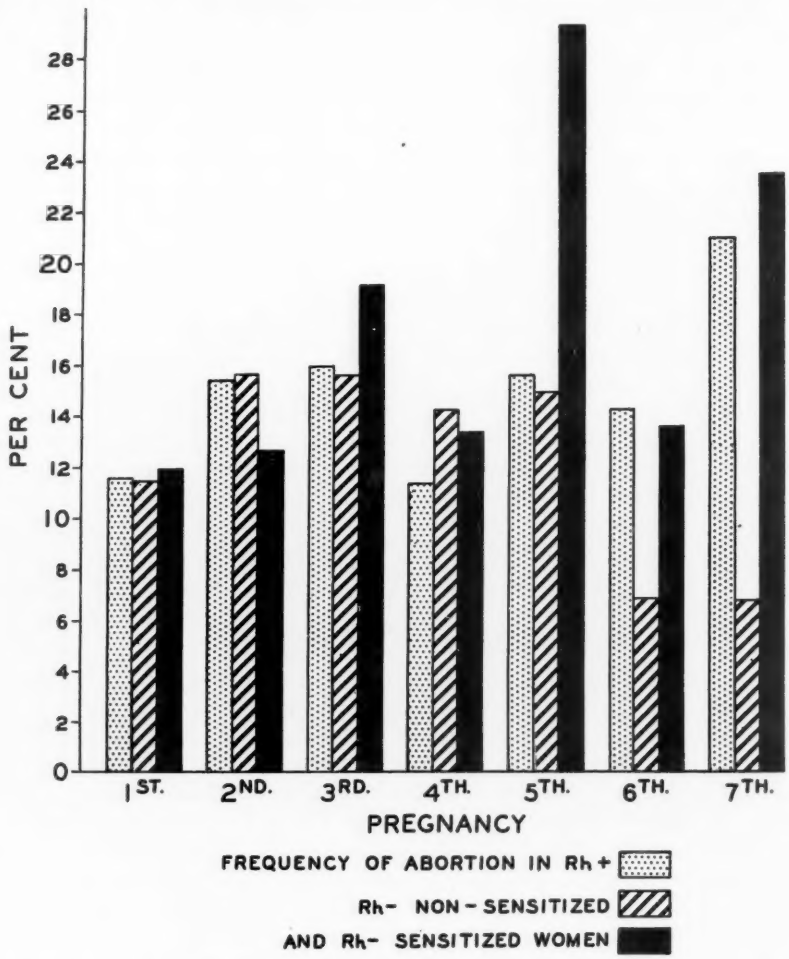

Fig. 1.—Frequencies of abortion in Rh-positive, Rh-negative nonsensitized, and Rh-negative sensitized women, by ordinal pregnancies.

For reasons previously pointed out, it would seem that all Rh-negative women might be considered together for their first through third pregnancies, for comparison with the Rh-positive group. The percentage of abortion for the combined first to third pregnancies, inclusive, for Rh positive and total Rh negative actually turns out to be identical (13.37 per cent).

A test for the significance of differences in the abortion rates for the several ordinal pregnancies may be made in spite of the complicating factor of the known increase in abortion frequency with advancing gravidity. This is performed by calculating the expectancy for women of each gravidity separately, on the general assumption that the incidence of abortions for women of any one gravidity is equally distributed among their pregnancies (1st to *n*th).

TABLE IV. TESTS OF SIGNIFICANCE OF DIFFERENCES IN ABORTION FREQUENCY AT DIFFERENT ORDINAL PREGNANCIES

	ORDINAL PREGNANCY							
	1ST	2ND	3RD	4TH	5TH	6TH	7TH PLUS	TOTAL
Rh+								
Expected	323.5	191.5	90	40	22	12	21	700
Obtained	291	193	100	37	33	16	30	700
Dev.	−32.5	+1.5	+10	−3	+11	+4	+9	
$\chi^2 = 15.34$; for 6 degrees of freedom, P = 0.02 − 0.01								
Rh− nonsensitized								
Expected	148	76	37	17	11	8		297
Obtained	134	86	41	19	12	5		297
Dev.	−14	+10	+4	+2	+1	−3		
$\chi^2 = 4.51$; n′ = 5; P = 0.50 − 0.30								
Rh− sensitized								
Expected	25	21	14	9	7.5	5	7.5	89
Obtained	25	18	17	7	11	3	8	89
Dev.	0	−3	+3	−2	+3.5	−2	+0.5	
$\chi^2 = 3.97$; n′ = 6; P = .70 − .50								

TABLE V. TESTS OF SIGNIFICANCE OF DIFFERENCES IN ABORTION FREQUENCY IN EARLIER VS. LATER PORTIONS OF PREGNANCY HISTORIES

A. *Ordinal pregnancy*

	1st + 2nd	3rd + all subsequent
Expected	515	185
Obtained	484	216
Dev.	−31	+31

$\chi^2 = 7.06$; n′ = 1; P < 0.01

B. *Gravidity classes*

	2	3	4	5	6	7	8	9+	
Expected	101.5	76	34.5	25.5	10.5	14	7.5	14.5	
Obtained (prior half history: latter half history)	84:119	67:85	33:36	20:31	4:17	11:17	5:10	5.5:23.5	
Dev.	+17.5	+9	+1.5	+5.5	+6.5	+3	+2.5	+9	
χ^2 =	6.12	2.12	0.12	2.38	8.04	1.28	1.66	11.18	Total 32.9

n′ = 8. P < 0.001

The results of this analysis are shown in Table IV. They clearly indicate that only in the Rh-positive group is there any real departure from expectation. For this group, the deviations from expectation are located chiefly in alternate pregnancies, the first, third, fifth, and seventh plus. The meaning of this becomes clearer if a different grouping of the data is adopted, as in Table V. First, the hypothesis that the early pregnancies (first and second) for women of all gravidity classes have a lower rate of abortion than later pregnancies (third and higher) is tested, and shown to be correct (Table VA). Then the slightly different hypothesis that the earlier half of the pregnancies of the women in each gravidity class (excluding primigravidas) has a lower abortion rate than the second half is likewise tested, and found to be quite beyond doubt. For every class, there is clearly a higher abortion frequency in the latter half of

the pregnancy history than in the prior half. This is apparent from an inspection of Table I, where the rate for the prior half of the histories is 14.7 per cent, and for the latter half 19.1 per cent. In Table VB, the actual values of abortion frequency in the Rh-positive women are compared with the values expected if abortion is equally frequent in prior and latter portions of pregnancy histories. The χ^2 values are particularly large for the ii-gravida, vi-gravida, and ix plus-gravida classes, being significant for each of these at the 1 per cent level. Since the difference holds true for each class, regardless of whether the gravidity is low or high, it may be assumed to mean that women have either an inherent or a psychologically conceived individual pattern of family size (i.e., number of pregnancies), and that as this is approached and exceeded, biological factors or voluntary actions tend more and more strongly to increase abortion. This is not a very startling conclusion, but it would appear to be the first time any quantitative evidence has been forthcoming to support it.

In the Rh-negative groups, no such relation is apparent. This is probably merely due to the statistical unreliability of small samples, inasmuch as the larger deviations, at least in the ii-gravida and iv-gravida classes of the nonsensitized group favor the latter half of the pregnancy history.

Summary

1. A total frequency of abortion of 15.44 per cent was reported in the 6,003 pregnancies of the 3,171 white women studied.

2. No significant increase in abortion was found in the histories of 209 Rh-negative sensitized women. A slight rise, if real, may be accounted for by the higher average number of pregnancies per woman in this class, in comparison with the Rh-positive and especially with the Rh-negative nonsensitized groups.

3. The analysis of 2,500 histories of Rh-positive women discloses a highly significant increase in abortion in the latter half history, irrespective of gravidity.

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INTERNAL PODALIC VERSION AND EXTRACTION

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INTERNAL podalic version and extraction is an obstetric procedure hallowed by time. However, proponents of routine versions have appeared at intervals to cause consternation and controversy in the medical profession, so that at the present time the value of this procedure is frequently overlooked. While it is true that a breech presentation is a major obstetric complication, the extraction following an internal podalic version is not the same for the three inherent dangers of breech extraction, namely extended arms, an extended head, and an unmoulded head, are usually avoided. When a high fetal or maternal mortality rate follows version and extraction, it generally means that the prerequisites and contraindications have not been observed, or the operator has had too little experience with the procedure. Extended or nuchal arms are almost always to be blamed on the operator. A timely version eases the accoucheur out of many a difficult situation. Especially is this true in the handling of inertial labors.

Material Studied

In the three and one-half years from Jan. 1, 1944, to July 1, 1947, 534 babies of 12,895 labors were delivered at the Elizabeth Steel Magee Hospital by internal podalic version and extraction. Twenty-eight of these were one of twins. This is a frequency of 4.1 per cent, or one version of every twenty-four deliveries. In comparison, Delfs and Eastman[3] report 0.9 per cent and Assali and Zacharias[1] 0.79 per cent. With this number of cases we feel qualified to speak on the merits and demerits of this procedure, for we have not the biased viewpoint of either the routine versionist or the inherent disbeliever in the operation.

Of the 534 patients, 495 were private and thirty-nine ward, including seventeen Negro patients. Of these, 436 deliveries were performed by obstetricians, including thirty-nine in consultation, twenty by men predominantly gynecologists, thirty-nine by residents, and thirty-nine by visiting staff members qualified to do operative obstetrics.

Age, Parity, and Term of Gestation

The ages of the patients varied between sixteen and forty-three, 245 patients being 30 years old or over. There were twenty-three primigravidas 35 years of age or older. Two hundred sixty-one patients were primigravidas and 273 multigravidas. The latter ranged from gravida ii to gravida xvii.

TABLE I. AGE DISTRIBUTION

AGE GROUPS	16-19	20-29	30-39	40-43
No. of cases	10	279	229	16

TABLE II. DISTRIBUTION BY GRAVIDITY

GRAVIDA	I	II	III	IV	V	VI	VII	VIII	XI	XII	XVII
No. of cases	261	138	82	28	10	4	3	5	1	1	1

All patients were at least four and one-half months pregnant, as shown in Table III.

TABLE III. TERM OF GESTATION

MONTHS	4½-5	5-6	6-7	7-8	8-9	9	9 PLUS
No. of cases	1	2	2	10	48	453	18

The pelvis was considered to be normal or gynecoid in 428 of the patients. The other types and corresponding fetal mortality, including that from intracranial hemorrhage, are shown in Table IV.

TABLE IV. "CLINICAL" CLASSIFICATION OF PELVIS

	NO. OF PATIENTS	MATERNAL DEATHS	FETAL DEATHS	INTRACRANIAL HEMORRHAGE
Gynecoid	428	1	23	7
Small gynecoid	23		2	0
Platypelloid	46		4	3
Anthropoid	14		0	0
Android	23		2	2

There are not enough cases of intracranial hemorrhage associated with the three abnormal types of pelves to draw definite conclusions, but the trend is in accordance with the generally accepted concept that the android pelvis is the most dangerous type for the performance of internal podalic version and extraction.

Indications

TABLE V. INDICATIONS FOR VERSION

INDICATIONS	NUMBER	MATERNAL DEATHS		FETAL DEATHS		
		NUMBER	PER CENT	NUMBER	PER CENT	
Inertia	220	1	0.45	12	5.4	
Persistent posterior	59			0		4.5%
Transverse arrest	50			3	6.1	
Failure of descent	24			1	4.1	
Prophylactic	92			3	3.2	
Relative disproportion	26			0		
Fetal distress or prolapsed cord	24			4	16.6	
Transverse presentation	13			1	7.6	
Face presentation	5			0		
Premature separation placenta	7			3	42.8	
Placenta previa	3			1	33.3	
Toxemia	3			1	33.3	
Abnormalities of cervix	5			0		
Hydrocephalic	2			2	100.	
Prolapsed hand	1			0		

There were fifteen indications given for performing version. The group composed of inertial labor, failure of descent, transverse arrest, and persistent posterior was by far the largest, accounting for 353 of the 534 cases. Frequently two of these were listed as indications, since they are usually complementary, but we have selected the one listed first on the chart for purposes of classification. Ninety-two versions, including twenty-six on a second twin were done "prophylactically." Most of these were multiparas, completely dilated, having poor

pains, and with the head high in the pelvis. Relative cephalopelvic disproportion accounting for twenty-six versions, fetal distress and/or prolapsed cord accounting for twenty-four versions, and transverse and face presentations accounting for eighteen versions were the remaining sizable categories. All other indications accounted for but a few cases each.

Not listed among the indications per se is a group of twenty-six attempted forceps. Many of these were consultation cases where attempted forceps had resulted in the head being pushed out of the pelvis or to a posterior position, and some were cases in which forceps extraction was considered to necessitate too much force for the welfare of the baby, and version was substituted as the safer method of delivery. Forty-two patients had been delivered by version previously, and one had had three previous versions.

Duration of Labor

The duration of labor is shown in Table VI. In 205 of the deliveries labor extended over eighteen hours, generally stated as the average duration of labor in the primigravida. The longest labor was one hundred and fifty hours. This confirms Rudolph's[10] contention that the "time element in a labor is of little value in determining the loss of uterine tone" and, accordingly, the danger of rupture of the uterus from doing a version.

TABLE VI. DURATION OF LABOR

HOURS	ALL CASES	PRIMIPARAS	MULTIPARAS
Up to 12	219	55	164
13 to 18	104	50	54
19 to 40	159	114	45
41 to 60	34	27	7
61 to 80	6	2	4
81 to 100	4	4	0
100 plus	2	1	1
Unknown	6	1	5

Ruptured Membranes

The membranes were definitely known to be ruptured prior to delivery in 254 cases. They were ruptured at delivery in 260 instances, and the status is unknown in twenty cases. The length of time ruptured membranes existed prior to delivery varied from one-half hour to five days.

TABLE VII. RUPTURED MEMBRANES

HOURS	NO. OF CASES	HOURS	NO. OF CASES
½ to 2	57	36 to 50	21
3 to 5	35	51 to 75	12
6 to 10	41	76 to 100	5
11 to 20	48	100 plus	3
21 to 35	32	Unknown	20

We do not feel that ruptured membranes are a contraindication to version. As long as the head can be easily displaced and the tonus of the uterine musculature is such that it will stretch adequately for internal manipulation a version can be performed without danger of rupture.

Complications of Delivery

Table VIII shows the complications encountered at the time of delivery.

Many of the cervical lacerations would have passed unnoticed, except for the fact that we examine all cervices in primigravidas and many in multiparas immediately following a version. The mention of Bandl's ring as a complication

means probably that the physiologic retraction ring was present in greater degree than usual, but obviously there could have been no true pathologic ring, or there would have been more ruptured uteri. There was only one ruptured uterus in this series, which is far below the number reported by Delfs and Eastman[3] or Cosgrove and associates[2] of 1:80 or 1:77 versions, respectively. Our patient was a 20-year-old unmarried Negro woman, gravida i, who started in labor at term. The pelvis was anthropoid, the length of labor forty-eight hours, and the membranes were intact with complete dilatation of the cervix. Due to inertia and a persistent posterior, the resident physician attempted delivery by version, but found a Bandl's ring prevented him from displacing the head. A staff man then attempted delivery, but in the effort ruptured the lower uterine segment transversely. The patient was taken to the operating room, and by lengthening the rupture a low cervical section was carried out. Plasma and penicillin were used, and mother and baby were discharged from the hospital in good condition after an afebrile postoperative course.

A previous section in two patients and a previous myomectomy in one were added risks of delivery.

TABLE VIII. COMPLICATIONS OF DELIVERY

Nuchal arm	3
Bandl's ring	26
2° laceration of perineum	169
3° laceration of perineum	7
Cervical laceration	30
Sulcus laceration	49
Manual removal of placenta	69
Packing of uterus	46
Plasma transfusions	18
Blood transfusions	1
Voorhees bag	3
Dührssen's incisions	1
Manual dilatation of cervix	10
Ruptured uterus	1

Piper forceps to the aftercoming head were employed in only twenty-nine instances, usually when manual flexion of the head proved difficult. We feel the use of forceps to the aftercoming head should be employed more often than in this series, so that flexion and extraction of the head can be carried out with less danger or damage to the fetus.

Postpartum Complications

There was one maternal death in the series. This patient, a 26-year-old, gravida i, was admitted to the hospital in inertial labor one week after her estimated date of confinement. After nine hours of labor the membranes were ruptured artificially, but the labor pains continued inertial in type. Thirty-six hours after the onset of labor she was completely dilated, and the baby was in a left occipitoposterior position. A fairly difficult version and extraction was performed, with delivery of a 7 pound 12 ounce infant. The patient was never fully aroused from the anesthetic, being markedly cyanotic. A medical consultant found moist râles and bronchial breathing in both lung bases, and diagnosed the condition as pulmonary atelectasis. The uterus remained firm, and there was no evidence of hemorrhage. Three and one-half hours after delivery the patient had a complete circulatory collapse and died. Permission for an autopsy could not be obtained. The infant died eighteen hours after delivery from a probable intracranial hemorrhage.

The other postpartum complications are listed in Table IX. A dilatation and evacuation was performed on the eleven patients with retained placental tissue as advocated in a previous paper.[5]

TABLE IX. POSTPARTUM COMPLICATIONS

Endometritis	16
Retained placental tissue	11
Acute mastitis	3
Breast abscess	1
Pyelitis	3
Thrombophlebitis	2
Herniorrhaphy	2
Bronchitis, atelectasis, and pulmonary edema	5

Four hundred forty-nine patients remained in the hospital twelve days or less; sixty-three between thirteen and fifteen days, and twenty-two for a longer period. The longest period of hospitalization was twenty-nine days for a patient with a thrombophlebitis of the left leg. There were sixty-six patients with a temperature of 100.4 or over for two consecutive days, not including the first twenty-four hours post partum. Forty-five of these were febrile for only two days. Of the eighty-five patients remaining more than twelve days in the hospital, sixty-six were afebrile.

Fetal Statistics and Mortality

There were 320 male and 214 female infants delivered by version and extraction whose weights varied from 12 ounces to 12 pounds 3 ounces.

TABLE X. WEIGHT OF INFANTS

WT. IN LBS.	0-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	11-12	12 PLUS
No. of cases	5	4	16	29	115	185	134	38	2	1

Thirty-one babies were lost. Sixteen of these were stillborn and fifteen neonatal deaths. This is a gross fetal mortality rate of 5.8 per cent. There were six monstrosities, four nonviable infants (under 3 pounds), and one macerated fetus. Also, in two cases of prolapsed cord resulting in stillborns, no fetal heart sounds were heard prior to delivery, and in a case of placenta ablatio the baby was delivered by version prophylactically after the placenta had been expelled. Thus the type of delivery was of no significance in these fourteen deaths, and accordingly, the corrected fetal mortality rate is 2.6 per cent.

TABLE XI. CAUSES OF FETAL DEATH

Nonviable	4	Separation of placenta	1
Monstrosities	6	Prematurity	3
Macerated	1	Prematurity and toxemia	1
Prolapsed cord	2	Prematurity and placenta previa	1
Intracranial hemorrhage	12		

The role of version cannot be proved in the five deaths attributed to prematurity. However, since prematures tolerate any handling very poorly, it is fair to suppose that the type of delivery was contributory to the deaths of these five infants all under 5 pounds in weight.

The twelve fetal deaths due to proved or probable intracranial hemorrhage are probably attributable to the version. Versions were performed in these ten primigravidas and two multigravidas for inertia, transverse arrest, or failure of descent. The membranes were ruptured from two to twenty-six hours before delivery in all but one instance, when they were ruptured at delivery, and the average length of labor was forty-one and one-half hours, varying from ten to one hundred thirty-four hours. The average weight of the babies was 8 pounds

2 ounces. Of the twelve patients delivering children dying from intracranial hemorrhage, nine were delivered by obstetricians (four in consultation), two by gynecologists, and one by the resident staff.

Besides the fatal injuries there were six infants with fractured clavicles, three with fractured humeri, four with brachial paralysis, and one with an intracranial hemorrhage. As far as known, none of these resulted in permanent injury or damage.

Discussion

Excluding the ninety-two "prophylactic" versions and extractions, the gross fetal mortality rate in this series was 6.3 per cent, and corrected 3.8 per cent. It must be remembered that each of these cases was a primarily difficult obstetric problem. The handling of inertia, persistent posterior, relative cephalopelvic disproportion, failure of descent, etc., is not easy. Only recently Schmitz and associates[11] reported a study of 224 cases of prolonged labor treated ultraconservatively (only three versions were performed) with a gross fetal mortality of 7.4 per cent (corrected 6.69 per cent). Statistics on high and midforceps are listed in Table XII.

TABLE XII

	HIGH FORCEPS DEATHS			MIDFORCEPS DEATHS		
	CASES	% FETAL	% MATERNAL	CASES	% FETAL	% MATERNAL
Kjelland[6]		4.54	0.91			
von Schubert[12]	50	6.	4.			
Martin[7]	67	30.5	7.5	193	8.7	0.5
Miller[8]	19	10.5		200	5.	
Assali	222	17.8	?	852	4.6	?

Available reports on version and extraction in recent years perhaps justify the apparent fear in which the operation is held.

		MATERNAL DEATHS		FETAL DEATHS	
	CASES	NUMBER	PER CENT	NUMBER	PER CENT
1940 Cosgrove[2]	221	2	0.9		30.8
1940 Miller[8]	76	0		25	32.8
1940 Martin[7]	38	2	5.2	15	39.4
1947 Assali[1]	120	2	1.6	44	38.7
1948 Present series	534	1	0.18	31	5.8

We do not understand the high mortalities shown in these reports. Most of our fetal deaths were due to errors in judgment, and such should get fewer with more experience. To cite one: a gravida iii, 31 years old, was followed through an uneventful pregnancy. Due to the fact that her babies were progressively larger (8½ and 11½ pounds) it was deemed advisable to induce her before term, particularly as she was an obese person (225 pounds), making it very difficult to correctly judge the size of the baby. Accordingly, at eight and one-half months the membranes were artificially ruptured and six hours later labor began. The pains were inertial in type and after nineteen and one-half hours the cervix was dilated completely, but the head was high and the

position posterior. A difficult internal podalic version and extraction was done, but instead of the 8- to 9-pound baby expected the infant weighed 12 pounds 3 ounces, and resulted in a stillbirth, obviously due to intracranial hemorrhage.

There was one ruptured uterus in this series of 534 versions. Delfs and Eastman[3] reports one in eighty at Johns Hopkins, and Cosgrove and associates[2] one in seventy-seven at the Margaret Hague. The reason for rupture in almost all cases, as in ours, is a tight ring which will not relax even with deep anesthesia, or a uterus moulded closely around the baby. Of course these are cases in which version and extraction should not be performed.

The chief contraindications to internal podalic version and extraction are:

1. Marked cephalopelvic disproportion.
2. True constriction ring dystocia.
3. A dry uterus moulded about the child.
4. Incomplete effacement and dilatation of the cervix.
5. Previous section or extensive myomectomy.
6. Placenta previa of any degree.
7. An inexperienced anesthetist.
8. Insufficient help.

Summary

A series of 534 internal podalic versions and extractions performed over a three and one-half year period is analyzed. They composed 4.1 per cent of all deliveries at the Elizabeth Steel Magee Hospital. Most of the patients were of private status, and all were delivered by or under the supervision of obstetricians, or by men with adequate training in obstetrics. Ages varied from 16 to 43 years, and gravidity from i to xvii. All but fifteen patients were of eight or more months gestation. Most of the pelves were gynecoid with the next largest category platypelloid. There were fifteen separate indications for version with the quartet of inertia, failure of descent of the head, transverse arrest, and persistent posterior the reason for 80 per cent of the versions. Over two hundred of the patients were in labor more than eighteen hours. In almost one-half of the cases the membranes were ruptured from one-half hour to five days prior to delivery. The complications of delivery included twenty-six marked physiologic retraction rings, one ruptured uterus, and seven third-degree lacerations of the perineum. Postpartum complications were not unusual, and only twenty-two of the patients remained in the hospital more than fifteen days post partum. There was one maternal mortality, and the gross infant mortality was 5.8 per cent, corrected 2.6 per cent; excluding the prophylactic versions and second twins 6.3 per cent and 3.8 per cent, respectively.

Conclusions

1. Internal podalic version and extractions should not be performed routinely.

2. There is no comparison between the dangers of breech delivery and extraction following an internal podalic version.

3. An android pelvis is the most dangerous type of pelvis for the performance of a version with regard to fetal mortality.

4. Many cases of inertia, failure of descent of the head, transverse arrest, and persistent posterior are best handled by version.

5. Premature rupture of the membranes does not contraindicate a version. The tonus of the uterine musculature and displacement of the head are the important criteria.

6. Routine mediolateral episiotomy and more frequent use of forceps to the aftercoming head are recommended.

7. Rupture of the uterus need not be a complication if gentleness and skill are practiced and contraindications to version adhered to strictly.

8. Internal podalic version and extraction is important in the armamentarium of the well-trained obstetrician. Obstetric residents should be trained in this procedure.

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MUCOCELE OF THE CERVICAL STUMP

Together With a Discussion of the Merits of Total vs. Supravaginal Hysterectomy

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NO REFERENCE to mucocele of the cervical stump could be found in a study of the literature. The amount of mucus coming from the cervix is variable and hard to measure. Viergiver and Pommerenke[1] have measured the amount of cervical mucus that could be aspirated at different times of the cycle. The maximum was from 200 to 700 mg. in weight. It is of interest that I was able to see the patient whose history follows a year before the condition to be reported had developed.

Case History

Mrs. S. K., a 41-year-old nullipara, married eight years, came to see me in March of 1946, complaining of slight postcoital bleeding which developed only two weeks before. The patient had had a hysterectomy performed in June of 1935, eleven years previously.

Examination showed a somewhat overweight woman who was somatically normal. There was a barely visible suprapubic median scar. Pelvic examination showed a nulliparous, uninfected introitus; a conical portio, the cervical stump being long, freely movable; no exudates. The adnexa could not be definitely outlined. The notation was made that the canal was almost obliterated. It did not bleed on examination or sounding. The patient was instructed to return if the bleeding recurred.

On June 25, 1947, after an interval of sixteen months, the patient was referred back to me by her physician who had been called to see her the preceding evening because the patient had expelled large amounts of clear mucus, two to three glassfuls, from the vagina. When the doctor saw her, there was still a large amount of mucus extruding. No bleeding, postcoital or otherwise had occurred since the patient had consulted me.

Her general examination was as before, the introitus nulliparous, the cervix high, the os somewhat patulous, the cervical stump seemed short, but there was a definite fluctuant resistance in the Douglas, more easily defined by rectal examination. On pressure, clear, thick mucus extruded from the external os. Introduction of a sound into the cervical canal showed a cavity about the size of an orange and was not followed by any bleeding.

The diagnosis of mucocele of the cervical stump was made, with the notation that an adenocarcinoma of the cervical canal would have to be looked for, as I had previously encountered a colloid cervical adenocarcinoma which secreted large amounts of mucus.[2]

On July 23, the patient was explored from below under general anesthesia, the operation consisting of an excochleation of the cervix. The vaginal mucosa at its junction with the portio was circumcised, the densely adherent bladder freed by sharp dissection. Posteriorly, the peritoneum could be pushed back until the very top of the pear-shaped mass was reached. During the manipulation, some five to six ounces of clear mucus extruded from the cervix. As the upper portion of the cervix was extremely adherent, after the canal had been split to make sure that there was no concealed carcinoma or other malignancy in the flaccid sac, the upper 1½ cm. of the musculature was left in situ with careful stripping out of the remaining mucosa.

The residual cavity between bladder and rectum was completely closed by several purse-string sutures and suture of the vaginal mucosa. The patient was discharged after seven days. Re-examination six months later showed a completely healed vaginal vault.

The removed specimen was a flaccid sac with walls in no place thicker than ½ cm., lined by a smooth mucosa, the arbor vitae having been entirely obliterated. The mucosa was intact except at the upper angle where it was complete but torn. Pathologic examination showed the epithelial lining to consist of a single layer of high epithelial cells with basal nuclei—typical cervix epithelium. Only close to the thinned out external os were deep-seated normal cervical glands noted.

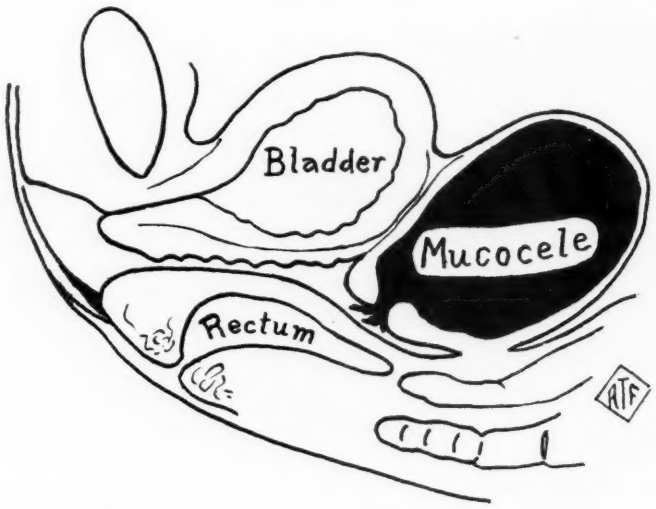

Fig. 1.—Schematic sagittal section of pelvis showing relation of distended cervical stump to pelvic viscera.

In a patient, twelve years after hysterectomy, the cervical stump, which one year previously was definitely normal in length, and had an almost obliterated canal, changed into a flaccid sac filled with clear cervical mucus and secreting mucus in large quantities. A report of the hysterectomy performed in June of 1935, received from the operating surgeon, said that the uterus was enlarged by multiple fibroids; that a supravaginal hysterectomy had been performed, both tubes and ovaries proving normal and being left in situ. The convalescence was uneventful, the patient being discharged on the fifteenth day. The patient had taken no estrogens or hormones of any kind. She did suffer from frequent flushes, although only 42 years of age. There is no explanation for this sudden change in the local situation. Evidently the somewhat stenosed canal did not permit of free drainage of the cervical mucus but what produced the sudden increase in secretion which, to my own observation, persisted at least between June 25, when I emptied the cervix by rectal and vaginal pressure, and the time of operation on July 23, when the cervix was again found to be completely ballooned, is not known. The histologic findings certainly in no way explain it.

Merits of Total Versus Supravaginal Hysterectomy

The case just presented, as well as others which I have encountered and have described,[3, 4, 5] raises the oft- and long-discussed question of whether complete hysterectomy is preferable to supravaginal amputation with preservation of the cervical stump.

Advocates of total hysterectomy base their preference in the main, on the fact that a number of cases are reported in which carcinoma has developed in the cervical stump. Polak,[6] as early as in 1920, was able to collect 256

cases of stump carcinoma from the American literature. Since then, a large number of additional cases have been noted. My personal experience covers only eight cases, not one of which was operated upon by me originally. In at least of these one of which was operated upon by originally. In at least one of these,[7] advanced carcinoma was discovered within five months of the operation, showing that the cancer had been overlooked at the time of the intervention.

It is my habit to study the cervix closely in patients in whom a hysterectomy is contemplated. Infection, erosion, polyps are dealt with appropriately so that at operation the cervix is healthy. In rare instances, normal conditions could not be restored and in these total hysterectomy was resorted to. It is my practice to cone out the upper 2 to 3 cm. of the cervical stump during supravaginal hysterectomy, thus passing the sutures, which close the stump, through cervical connective tissue devoid of mucosa. Such a procedure in itself might have prevented the formation of the mucocele just described.

In several instances I have been confronted with complete prolapse of the cervical stump. In every one of these, I have been able to obtain a permanent cure of the prolapse by means of the Manchester operation. In an approximately equal number of total eversions of the vagina following complete hysterectomy, I have been obliged to perform colpocleises to hold back the prolapse in old women, or to resort to palliation by means of the use of a Gellhorn pessary, after building up the perineum in younger patients.

Moreover, I have been consulted by an increasing number of women who complain of pain, dysuria, dyspareunia, and dryness of the genitals following complete hysterectomy. In them I find scarry, often unduly short and dry vaginal canals. I know of no means of relieving their symptoms adequately. In addition, I encounter an undue number of vesicovaginal fistulas following the total operation. I instance these sequelae because the statistically minded assure us that total hysterectomy entails no increase in mortality and but little increase in morbidity in skilled and experienced hands.

The somewhat hysterical overanxiety to ferret out cervical cancers *in situ* or often only *in prospect,* now current, is a perhaps justifiable reaction against the callous myopia, carelessness, and ignorance which for years exposed womanhood to unnecessary danger and neglect by omitting even vaginal examination because of "delicacy." Today we see the opposite picture, namely, women racked by unjustified fears, anxieties, and premonitions of disaster caused by the witch-hunter attitude of the professional cancer tracker. A careful, thorough, but less dramatic and disquieting approach is called for without deliberately alarming the woman who presents herself for her yearly checkup. Cytologic examination of the cervical and vaginal discharges is laudable if confined to competent hands. Postive findings warrant further investigation (biopsy and curettage). My interpretation of metaplastic changes is far less radical than the present ones current. In defense of my conservative attitude—if defense is necessary—I may say that my over forty years' experience coincides *exactly* with that of Dr. J. Heyman of Stockholm, Sweden, who has been in charge of the gynecologic clinic at the Radium-Hemmet since 1914, who, in a discussion of Ayre's[8] paper, at the meeting at Atlantic City said, "At the gynecology clinic of Radium-Hemmet in Stockholm, we see a great number of patients with cancer of the uterus. We also see a great number of patients with irregular bleeding, and a number of patients are annually referred to us suspect of having a uterine carcinoma. Sweden is a sparsely populated country, and it is easy for us to follow all the patients referred to us. And we do follow them. Since 1914, any patient of the type mentioned who was

referred to us has been followed. Our follow-up is 100 per cent. It is a fact—and I think a rather surprising fact— that *a carcinoma has never developed in a patient in whom we failed to diagnose the cancerous lesion on clinical examination or on biopsy.* There seems to me thus to be *some slight''* [all the italics are mine] ''discrepancy between the experience of the cytologist and the clinician.''

In view of the above facts and observations, I continue to perform supravaginal amputation for benign lesions. Only in rare instances, if the cervix cannot be restored to a sufficient degree of normalcy, do I resort to total hysterectomy. In the presence of malignancy—corpus carcinoma or sarcoma—the radical Wertheim technique is indicated. For carcinoma of cervix, I perfer radio therapy alone, after trial of radical operation following completion of radiotherapy, without improvement of results.

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ABDOMINAL CYSTOCELEOPLASTY

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A CYSTOCELE may be defined as a true hernia of the bladder through the pubocervical fascia and anterior wall of the vagina. These layers between the vagina and bladder are important in forming a hammock for the bladder and the disruption of this eventually leads to a cystocele. This is usually caused by the prolonged stretching of the vagina and its covering beyond its threshold of resilience during parturition and the fascia remaining permanently relaxed. The thinned attachment of the pubocervical ligament may be torn completely from the cervix. It is at this point where the majority of cystoceles observed protrude through the fascial barrier near the attachment of the cervix and at the proximal part of the vagina.

In its early stage, the cystocele is usually rather small and customarily, solitary in nature. However, if one should intelligently evaluate the potentialities, he would find that the cystocele may become progressively larger with age. The etiological factors mainly responsible for the progressive development of the hernia are the increased intra-abdominal pressure resulting from defecation and urination and the gradual decrease in tonicity of the ligaments which occurs with the climacteric. As a person becomes older, the ligaments become more lax and flaccid, and yield to stress and strain much more easily. If this process continues long enough, the entire length of the pubocercival fascia becomes involved, and when the area in the region of the neck of the bladder yields, it gives rise to an urethrocele. If one could correct the defect in its early stages, he might easily prevent the formation of a large cystocele with a complicating urethrocele in later life. Ordinarily, one would not attempt to repair a small or moderate sized cystocele from below, as usually it does not cause any symptoms at this time. Secondly, the procedure is often rendered difficult because of its inaccessability due to the high fixation of the cervix. Normally, the gynecologist undertakes correction of the cystocele when it has become rather large and is the cause of troublesome urinary symptoms such as stress incontinence, frequency, urgency, etc. Any procedure which repairs the rent in the pubocervical fascia, thereby creating a strong bladder floor, will remedy the cystocele. Everyone concedes that this is most easily accomplished by the vaginal route in the large baggy types of cystoceles complicated by a urethrocele. Also, there is no doubt that the Manchester type of vaginal repair restores the structures more nearly to their anatomic position than any other type of procedure. Operations, such as suspension of the uterus, hysterectomy, shortening of the round ligaments, ventral fixation, etc. do not correct the cause of the hernia and are used injudiciously. Many authors add that cystoceles can be repaired only from below. It can be wisely stated that in the majority of cases this is quite true, as usually the gynecologist is not consulted until the hernia is quite large and is causing annoying symptoms.

Frequently, however, one is confronted with a patient who has a valid indication for an abdominal operation and has also a small to a moderate-sized cystocele. This multiplicity of pathologic conditions is not unusual and, in my

experience, there is a fairly high incidence of pelvic disease associated with cystocele. It is necessary, therefore, to operate abdominally, as well as from below, in approximately 25 per cent of the cases. For example, in the presence of an ovarian tumor, chronic diseases of the tubes, uterine fibroids, retroverted uterus in the childbearing period, etc., in conjunction with a cystocele, it is considered essential to combine a vaginal approach with an abdominal laparotomy. This double procedure taxes the patient no end, as there is considerable time lost in the preparation of the patient and surgeon in making ready for the second operation. More valuable time is lost in exposing the structures from below when these same tissues may have been partially displayed during the initial operation. For example, in doing a supravaginal hysterectomy or panhysterectomy, the pubocervical fascia is readily exhibited in its superior portion when the bladder is stripped off of the cervix and vagina. When a bladder retractor, is placed into position, the entire bladder floor along with Mackenrodt's ligament may be demonstrated.

The operation described in this paper is not intended to supplant any of the time-honored procedures used in the repair of cystoceles. Rather, it is intended solely for the correction of a cystocele, from within the abdomen, in those cases in which a laparotomy is imperative for the correction of other pathologic manifestations in the pelvis and it should be reserved for small or moderate-sized cystoceles. It should be done chiefly as a prophylactic measure during the course of other abdominal operations with the intention of preventing progressive dilatation of the fascial defect. It should be resorted to only under these conditions and one should refrain from applying it routinely to all types of cystoceles. In young women, in the childbearing period, who present the triad of retroverted uterus, partial prolapse, and a moderate-sized cystocele, it should be the operation of choice. One may repair the hernia by suturing the defect in the pubocervical fascia, suspend the uterus by the modified Gilliam technique, and augment the prolapse by parametrial fixation and plication of the uterosacral ligaments. All this may be done abdominally and at one session.

In abdominal cystoceleoplasty, one deals with the same structures as in any other cystocele repair; namely, the pubovesicocervical fascia. The difference, of course, lies in the fact that one approaches the structures from above instead of from below. If it is not necessary to disturb the uterus during the course of the operation, one may easily expose the same fascial structures by dividing the uterovesical peritoneum transversely along its attachment to the uterus and extending the incision out along the broad ligaments. The bladder is separated by blunt dissection from the lower segment of the uterus, the cervix, and the vagina. This is facilitated by using a sponge stick and gradually stripping the bladder away from its attachment to the genital tract practically to the urogenital diaphragm. Tugging on the uterus or cervix in an upward fashion causes tension on the anterior wall of the vagina and pulls the urethra from under the pubic bone. In this manner, dissection and mobilization of the neck of the bladder may be done expediently. A narrow bladder retractor is used to elevate the bladder and the pubocervical vesical fascia along with the pillars or lateral ligaments of the bladder are easily disclosed. The thickened portions of the pubocervical fascia lying along the anterolateral portions of the vagina are grasped with Allis clamps and brought together with interrupted No. 1 chromic catgut sutures. These are placed consecutively in such a manner as to approximate the fascia in the midline and obliterate the hernial defect. Traction on each successive suture facilitates exposure. They should be placed progressively and extend as far forward as possible to the posterior surface of the

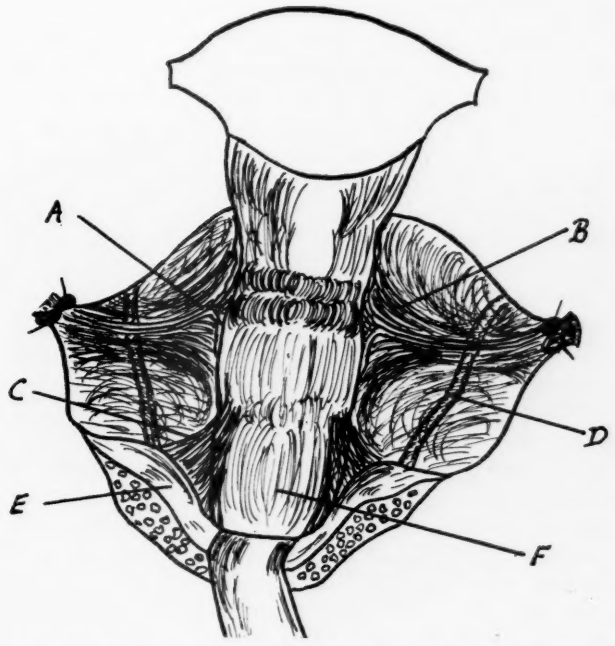

Fig. 1.—Schematic drawing showing exposure after vesicouterine peritoneum and bladder is stripped off the uterus, cervix, and vagina. A-Uterine vessels. B-cardinal ligament. C-Lateral ligaments of the bladder. D-Relative position of ureters. E-Bladder. F-Pubocervical fascia.

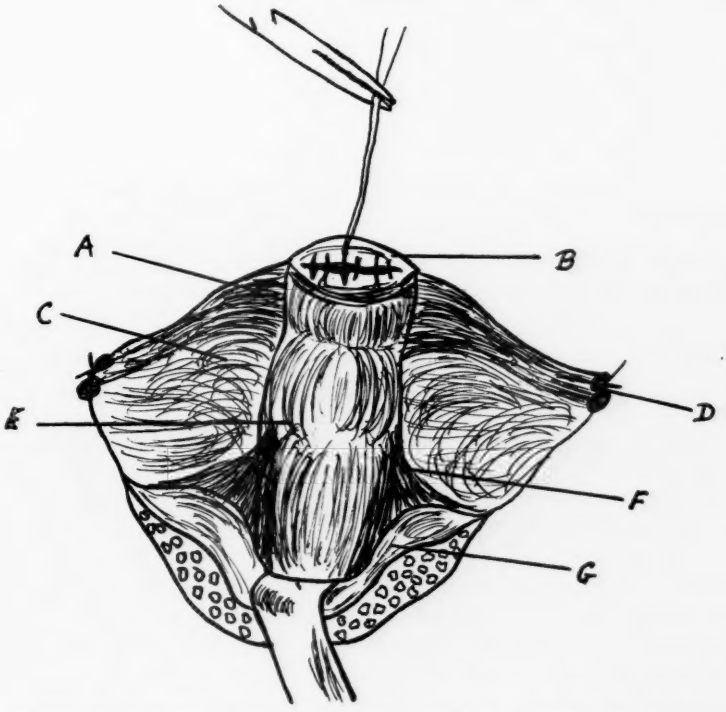

Fig. 2.—Schematic drawing showing exposure during a supravaginal hysterectomy. A-Cardinal ligaments of Mackenrodt. B-Cervix. C-Parametrium. D-Stumps of round and broad ligaments. E-Pubocervical fascia. F-Lateral ligaments of the bladder. G-Bladder.

neck of the bladder. Parametrial fixation of the cardinal ligament of Mackenrodt may also be carried out with little difficulty. A mattress suture of No. 1 chromic catgut is placed in the parametrium on each side of the cervix in such a fashion that when the suture is tied, it fixes the condensation of fascial fibers anterior to the cervix. This procedure shortens the overstretched cardinal ligaments and overcomes the partial prolapse of the uterus. If additional support is needed, the uterosacral ligaments may be plicated to add further strength to the supporting structures. By this method, a moderate-sized prolapse may be corrected effectively and practically. The entire area is then peritonealized with the uterovesical peritoneal flap, either in a manner following a hysterectomy if the uterus was removed, or in a manner similar to the peritonealization used during a low cesarean section.

One is certain to ask what happens to the puckered vaginal mucosa after the vagina is narrowed from side to side. In my experience, the redundant vaginal wall retracted and involuted in six to eight weeks. This was due evidently to the rather elastic nature of the vaginal wall which contains involuntary muscle fibers in addition to fascia. Apparently, these fibers contract and, after a short period of time, the normal contour of the vagina is restored. There are several conditions which might interfere considerably with the operative technique. Obesity of patients or extremely deep pelves may prove to be almost unsurmountable obstacles and impede efficacious completion of the operation. Also, one should not attempt to correct a large cystocele complicated by an urethrocele which presents symptoms of stress incontinence. Exposure of the vesical neck is usually rather difficult and plication of the urethral sphincter is an impossibility.

Conclusions

1. Cystoceleoplasty by the abdominal route is not only feasible but the results are entirely satisfactory and compare favorably with other cystocele repairs.

2. The operation can be performed without much difficulty while repairing other pathologic conditions in the pelvis and much time can be saved by adopting this procedure.

3. Moderate degrees of prolapse of the uterus may be corrected concurrently by shortening the cardinal and uterosacral ligaments.

4. Certain conditions such as obesity, extremely deep pelves, or large cystoceles with complicating urethrocele and symptoms of stress incontinence may be considered valid contraindications for the performance of the operation.

CASE 1.—M. A., aged 36 years, was admitted to Harford Memorial Hospital on Jan. 7, 1948, complaining of pains in the lower abdomen, irregular menstrual periods, a sense of pressure in the pelvis, and a feeling as if everything were falling out. General physical examination was essentially negative. Examination of the abdomen revealed it to be flat; liver, spleen, and kidneys not palpable. There was a lower right rectus well-healed scar. Moderate diffuse tenderness was noted in both lower quadrants; no rigidity or palpable masses. Examination of the pelvis disclosed the external genitals to be normal; Bartholin's and Skene's glands not palpable. The outlet was marital, multiparous with moderate relaxation of anterior vaginal wall and slight relaxation of posterior vaginal wall. The cervix descended somewhat on straining and appeared healthy. The uterus was normal in size, shape, position, and contour. Both adnexa were somewhat enlarged, fixed, and tender. The preoperative diagnosis was chronic pelvic inflammatory disease, (bilateral), cystocele (moderate), and prolapse of the uterus (first degree). Laparotomy was done on Jan. 8, 1948, and the

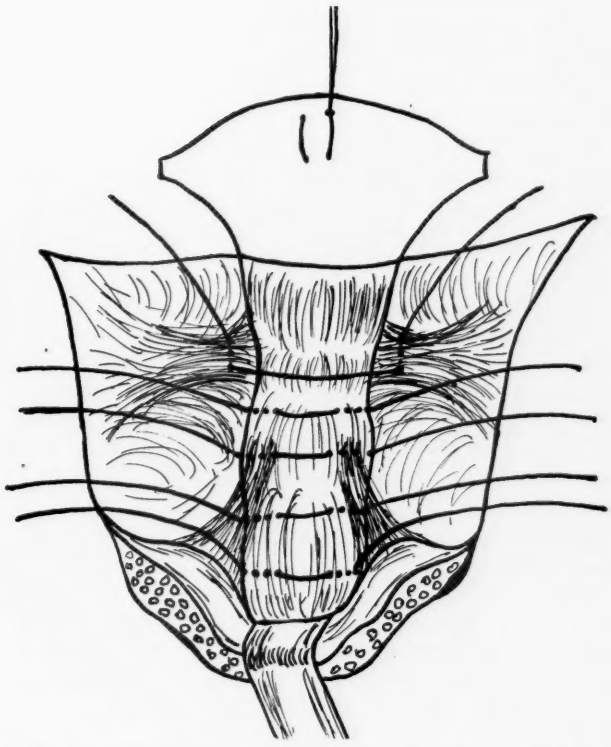

Fig. 3.—Schematic drawing showing interrupted sutures placed in the pubocervical fascia on the anterolateral portion of the vagina. A mattress suture has been inserted into the cardinal ligament on each side of the cervix.

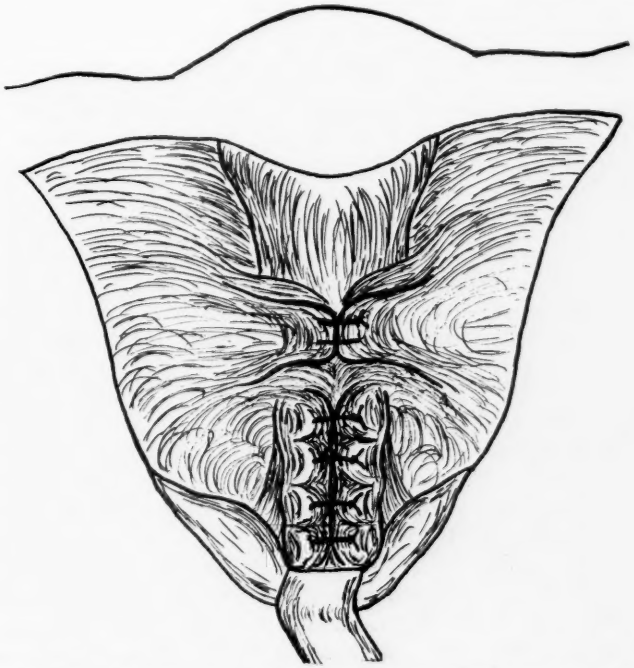

Fig. 4.—Schematic drawing showing the cardinal ligaments fixed anterior to the cervix and the pubocervical fascia plicated in the midline.

uterus was found to be normal in size, shape, and position. Both tubes were convoluted, dilated, clubbed, and fixed to the broad ligament. The ovaries were essentially normal. The appendix had been previously removed. A bilateral salpingectomy and an abdominal cystocele oplasty were done along with parametrial fixation of the cardinal ligaments and plication of the uterosacral ligaments. The postoperative course was afebrile after the second day and the patient was discharged on the seventh day in good condition. Pelvic examination after six weeks revealed the vaginal wall normal in contour and there was no bulging on bearing down. The sense of pressure in the pelvis was no longer present and the patient stated that she felt quite well.

CASE 2.—P. H., aged 24 years, was admitted to Harford Memorial Hospital on Jan. 14, 1948, complaining of pains in the lower portion of the back and continuous bleeding of twelve weeks' duration. This had varied from a profuse reddish brown discharge to a bright red free bleeding. General physical examination was essentially negative. The abdomen was flat; liver, spleen, and kidneys not palpable. There was moderate diffuse tenderness in the lower abdomen, especially over McBurney's point; no rigidity or palpable masses. Examination of the pelvis disclosed the external genitals to be normal. The outlet was marital, multiparous with moderate relaxation of anterior vaginal wall. The cervix appeared slightly hypertrophied but healthy in appearance. The uterus was slightly enlarged and moderately irregular. It was noted that the right adnexa were slightly enlarged and tender. Left adnexa negative. The preoperative diagnosis consisted of uterine fibroids (small), chronic appendicitis, and cystocele (moderate). A dilatation and curettage were done and the body cavity of the uterus was found to be rather irregular. On laparotomy, it was noted that the uterus was enlarged and the contour was slightly lobulated. Both tubes were normal. The right ovary contained a corpus luteum. The left ovary was normal. Since the patient had three children and since the question of further childbearing was unimportant, a supravaginal hysterectomy was done. Following this, an abdominal cystoceleoplasty with plication of the uterosacral ligaments was carried out. The appendix was about 7 cm. long, moderately injected, and bulbous at the tip. This was removed in the routine manner. The postoperative course was uneventful and the patient was discharged on the eighth day in good condition. Pelvic examination after six weeks revealed the cervix to be well supported and the anterior vaginal wall was smooth, firm, and well bolstered.

CASE 3.—M. M., aged 35 years, was admitted to Bon Secours Hospital on Feb. 8, 1948, complaining of pain in the right lower quadrant, and intermittent attacks of nausea. During the past two years, she complained of frequency and urgency with inability to empty the bladder completely. Patient had a nephropexy done one year ago without relief of symptoms. General physical examination was essentially negative. The abdomen was normal, liver, spleen, and kidneys not palpable. There was a right well-healed kidney scar. Moderate tenderness was noted over McBurney's point; no rigidity or palpable masses. Examination of the pelvis disclosed normal external genitals. The outlet was marital, multiparous with moderate relaxation of anterior vaginal wall. The cervix was small and slightly eroded. The uterus was found to be retroverted (second degree); both adnexa were prolapsed but neither were enlarged nor tender. The preoperative diagnosis was retroverted uterus (second degree), chronic appendicitis, and cystocele (moderate). A laparotomy was performed on Feb. 9. 1948, and it was noted that the uterus was partially retroverted with both adnexa prolapsed. There was a slight descensus of the pelvic organs. An abdominal cystoceleoplasty with parametrial fixation was done by the usual technique, after which, a modified Gilliam hysteropexy with plication of the uterosacral ligaments was carried out in the customary manner. The appendix was moderately injected throughout and the distal half was rather thick walled and contracted. This was removed and the stump inverted by pursestring. The postoperative course was essentially uneventful and the patient was discharged on the tenth day in good condition. Examination after six weeks revealed the bladder to be well supported and the mucous membrane of the anterior vaginal wall had involuted completely. Patient was symptom free and felt quite well.

THE THIRD STAGE OF LABOR
A PLEA FOR MANUAL REMOVAL OF THE PLACENTA

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THE third stage of labor has repeatedly been the subject of much discussion and dissension, yet is the least understood and most ill managed and the most tampered-with stage. We are told that the persistence of postpartum hemorrhage is due to mismanagement of the third stage and that most deaths are preventable. If our teachings have been at fault, surely this can be corrected.

The practice of massaging and squeezing the uterus after the birth of the baby to separate the placenta, as well as the less traumatic plan of holding the fundus are mentioned only to be condemned. By such procedures, nothing is gained and much is lost by unnecessary traumatism. They may result in partial detachment of the placenta with more bleeding, hence it is far preferable to wait for clinical signs of separation than to hasten it by Credé's compression. The ecchymotic and contused abdominal walls, the sensitive and bruised uterus, and the relaxed and tender uterine ligaments are familiar observations. There is little wonder that manual removal of the placenta under such circumstances carried a bad reputation. Paddock calls our attention to the fact, "modern methods of amnesia, analgesia and anesthesia tend to make the third stage unphysiologic. . . . It takes longer for the patient to marshall her normal powers of response. The uterus is flaccid and will not respond to stimulation quickly. Hence, any attempt to separate or remove the placenta would be expected to result in increased bleeding, without the normal hemostatic effect of the contractile uterus." While the writer does agree that general anesthesia and large doses of sedatives do delay the speed of placental expulsion, and even in some cases interfere with its completeness, he feels that Ergotrate, properly timed, and given intravenously as soon as the baby's head is born, and given in large doses (i.e., never less than 1/160 grain), restores the mechanism of uterine contractability to normal within a matter of 20 to 30 seconds.

It must be remembered that the placenta, even under deep anesthesia, separates by itself very shortly after the baby is born. It's expulsion, however, under general anesthesia, is delayed, hence it is obvious that anesthetized patients must be given an oxytocic. The writer feels that if the empty uterus is immediately lifted high out of the pelvis by pressure through the anterior abdominal wall and the elevated uterus is held in this position by a hand

which grasps and lifts the lower uterine segment against the spinal column and if another hand compresses the fundus, with or without massage (usually without), it will be a matter of a few minutes until retraction of the uterine fibers will occur, bleeding will stop, and the uterus and cervix will return to normal. Vigorous massage and compression in anteflexion or continuous massage on the uterus which is already firm do more harm than good.

Sewell and Coulton speak of "Manual Removal of the Placenta, as a Benign Procedure." They stated, "Not many years ago, manual removal of the placenta was considered one of the most deadly and dangerous procedures that obstetricians could be called upon to perform and the average mortality ranged from 10 to 15 per cent."

TABLE I. MANUAL REMOVAL OF PLACENTA

REPORTED BY	TOTAL DELIVERIES	TOTAL MANUAL REMOVALS	PER CENT INCIDENCE	PER CENT MATERNAL MORTALITY	PER CENT MATERNAL MORBIDITY
L. D. Odell and W. F. Hovis, Iowa City, Surg., Gynec. & Obst. 77: 553, 1943.	15,824	70	.25	2.8	----
Dawson, Univ. Otago, New Zealand, M. J. 43: 7, 1944.	6,000	40	.66	2.5	5
Schwartz and Richards, Bellevue Hosp., AM. J. OBST. & GYNEC. 45: 235, 1943.	8,902	74	.83	2.7	43.1 Uncorrected
J. L. Ahumada and J. Diradourian, Arch. Clin. obst. y. ginec. "Eliseo Cantón" 1:200, 1942.	5,280	702	1.3	8.1	----
J. P. Clerc, Univ. Geneva, Gynaecologia 121: 213, 1946.	6,973	100	1.4	0	14 Corrected
R. E. Arnell and R. F. Phillips, Charity Hosp. of Louisiana, South. M. J. 34: 598, 1941.	-----	152	---	6.5 Gross 1.9 Corrected	----
C. H. Peckham, Bull. Johns Hopkins Hosp. 56: 224, 1935.	From 1896 to 1933	186	1.2	10.76 if operative del'y, 4.48 if spontaneous	48.48 10.45
A. Montag, Monatschr. f. Geburtsh. u. Gynäk., Feb., 1926.	15,100	147	1.02	4.76	30.6
W. J. Dieckmann et al., Chicago Lying-in Hosp., AM. J. OBST. & GYNEC. 54: 415, 1947.	6 months, 1946	80	---	0	7.9
	6 months, 1945	18	---	0	9.2

It has been claimed that the more infected the patient was at the time of removal, the greater the danger of manual removal. Is this actually true? This has not been my experience. Waters and Norton and others, who remove the placenta manually in their extraperitoneal cesarean sections in patients already infected do not report that the procedure is risky. If it is not a dangerous procedure to remove the placenta in frankly infected cases that are subjected to the extraperitoneal operations, why should there be any greater danger in removing the placenta vaginally? Is it not logical to suppose that the operative procedures which are used to remove the fetus together with the blood loss incurred from trauma increase the incidence of sepsis, rather than the manual removal of the placenta itself?

Obstetricians are now teaching earlier manual removal. Stoeckel taught, "Manual removal of the placenta should be done earlier and more frequently than it has been done." Greenhill remarks, "The evil consequences of manual removal of the placenta are usually due to procrastination. In hemorrhage, due either to uterine atony or laceration after delivery of the baby, the placenta should be removed without delay and not after the patient has lost too much blood." If an obstetrician knows and practices proper asepsis, he can safely invade the cavity of the uterus.

Marked differences of opinion by experts only confuse the students. It is my opinion that if students were taught immediate manual removal of the placenta with strict attention to asepsis and gentleness, much blood could be saved in those cases that are already under anesthesia.

Dieckmann has been advocating manual removal of the placenta for many years and he recently reported 80 manual removals of the placenta and 12 explorations of the uterus for a six-month period in 1946, which he compared with 18 manual removals and 2 explorations done during a similar length of time in 1945, and found that the hospital morbidity was 7.9 per cent in 1946 and 9.2 per cent in 1945. He stated, "We believe that the only way to learn to remove the placenta manually is to do it in normal cases under supervision." The dicta that "the only safe uterus is an empty uterus," that "the empty uterus will not bleed," that "the time to stop a postpartum hemorrhage is before it begins," that "the uterus can be invaded safely when this is performed aseptically," and that, other things being equal, "a short third stage should have less blood loss than a long third stage" have been responsible for the writer's unorthodox practice of immediate manual removal of the placenta in all of his last 1,625 anesthetized patients. All of the cases reported have been delivered by the writer at the Columbus Hospital in Newark, New Jersey.

TABLE II. TOTAL NUMBER OF CASES—1,625

1. Forceps	818
Number deliveries, full term	602
Premature, 7 to 8½ months	65
Version and breech extraction	21
Breech extraction	75
Twins	26
Erythroblastosis	4
Dührssen's incisions	2
Face presentation	5
Anencephalus	4
Hydrocephalus	1
Transverse presentation	2
Total	1625
2. Maternal mortality	0
3. Maternal morbidity	0
4. Number requiring tamponade	3
5. Number of placenta found adherent	7
6. Number of delayed postpartum hemorrhages, 5 to 21 days	4
7. Number requiring transfusions for postpartum hemorrhage	None

The technique utilized does not differ from the classical descriptions given by most textbooks. Immediately after the delivery of the baby, the gloved hands are thoroughly soaked in a weak Lysol solution. The hand used to re-

move the placenta is freely lubricated with tincture of green soap. The parturient canal is carefully checked for lacerations, tumors, uterine inversion, etc. The position, degree of placental separation, and denseness of placental adhesions are noted as the placenta is removed. In only 16 cases (1 per cent), was the placenta found completely separated and loose in the vagina. In all others, the placenta was still attached to the uterus. However, in 408 cases (25.1 per cent), the lower placental edge was partially separated for a distance of one to two inches. It is evident that all of these cases required further manual separation of the placenta to complete the process.

An analysis of Table II shows the maternal morbidity reported by the writer as zero. The puerperal morbidity for the 1,625 cases was 4.6 per cent. Since the writer could not find a single case where the procedure of manual removal of the placenta was responsible for the puerperal morbidity, this figure of zero seems justified.

In the writer's experience, routine manual removal of the placenta has reduced the incidence of postpartum hemorrhage, has decreased the incidence of delayed puerperal hemorrhages (5 to 21 days post partum), has kept blood loss at a minimum, has not increased the incidence of puerperal morbidity, has made the operator the master of the third stage, not its timid observer, has enabled careful exploration of the uterus; has not been accompanied by a single case of uterine inversion; and has prepared for the packing of those rare uteri which continue to bleed after placental separation—i.e., abruptio placentae, placenta previa, pathologically adherent placentas, etc. By careful exploration at this stage, one can detect placenta increta, submucous fibroids, uterine, cervical, and vaginal tears requiring sutures, constriction rings, threatened uterine rupture or inversion, undiagnosed twins, etc. The writer has been able to check up on the statement that "a patient who has had one manual removal of the placenta is likely to require another removal in subsequent pregnancies." This statement I have found to be correct. The placenta is not infrequently more densely adherent in subsequent removals, but not always. I have also been impressed by the increase in the delay in the third stage of labor in many cases of prematurity and immaturity of the infant and maceration of the fetus. Twin placentas by their huge size are often a cause of delayed third stage. It may also be stated that the larger the weight of the baby and placenta or the area of maternal surface of the placenta, the greater the loss of blood. An exception to this is the larger edematous placenta of hydrops fetalis. It has also been my finding that difficult operative procedures, prolonged labors, and amnion sac infections cause delay in the third stage of labor. Placental abnormalities, i.e., tubocornual placentas, bilobate, membranacea, succenturiata, etc., have also been responsible for delayed placental stage. While all these factors are important, I have been impressed by the fact that, in the majority of the cases where I have been called in consultation, mismanagement of the third stage, with resulting hemorrhage and placental retention due to constriction ring of the uterus, has been the commonest cause. In these cases, morbidity was directly related to the degree of hemorrhage and shock.

Comment

The purpose of this paper is to enter the plea for earlier manual removal of the placenta. It is my conviction that the procedure of manual removal of the placenta has been unfairly condemned. The bad results of this procedure have been measured by the worst emergencies for which it is undertaken,

hence its reputation as a serious operation. It is my belief that the routine and immediate removal of the placenta in the already anesthetized patient is a harmless and rational procedure when performed by men adequately trained in its performance. In the past, we have suffered from too rigid an interpretation of the indications for removal. More radical liberalization of indications for manual removal of the placenta are in order. I do not expect that most obstetricians will agree with my practice, but I feel that a more generous resort to the procedure recommended will greatly reward those who are bold enough to try it. A word of caution is necessary. Until this practice of mine has been thoroughly checked by several major maternity hospitals, I would not recommend its general use by the average practitioner. In the hands of men properly trained, immediate routine manual removal of the placenta in the anesthetized patient is a safe practice.

Conclusions

One thousand six hundred twenty-five cases of manual removal of the placenta performed by the writer in his private practice are reviewed. The mortality of the procedure was zero. The morbidity was no higher than that seen in normal vaginal deliveries without resort to removal of the placenta. Because of prompt removal of the placenta, the uterus contracts more quickly and firmly. The blood loss was less than that seen where compression and expression of the uterus were resorted to. The number of cases requiring uterine tamponade has decreased considerably since this practice was followed. The procedure of manual removal of the placenta is still notoriously bad in its results when performed on the shocked and exsanguinated patient.

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SPECIFIC ESTROGENIC AND ANDROGENIC SMEARS IN RELATION TO THE FETAL SEX DURING PREGNANCY*

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IN A STUDY of vaginal spreads from some 2,500 women, it appeared that cytolysis was an estrogenic effect while the presence of mucoid material with increased cornification indicated androgen activity. A survey of 253 pregnant women during all stages of pregnancy revealed a close correlation of the androgenic and estrogenic smear to the fetal sex.[7]

The evaluation of estrogenic activity by the vaginal smear is based on the amount of cornification present.[1-5] The frequent occurrence of spreads with increased numbers of Döderlein bacilli or complete destruction of cytoplasm has been intriguing. Little attention has been paid to the presence of mucoid material.

The purpose of this paper is to present data on a new series of 89 pregnant women, in whom vaginal smears were taken at various stages of pregnancy.

Method of Investigation

Vaginal smears were taken in 89 women during various stages of pregnancy. Desquamated cells from the vaginal epithelium were obtained by insertion of a cotton applicator into the vault of the vagina. The staining procedure employed was that of hematoxylin and carmine for the additional evaluation of glycogen.

Results

The effect of pregnancy on the vaginal epithelium is essentially a progressive increase in proliferation and glycogen deposition, due to augmented estrogen production. Increased progesterone activity causes more rapid desquamation of epithelial cells. The vaginal smear at any time during pregnancy will thus reflect the state of estrogen-progesterone activity. The main characteristic changes in the smear are a progressive increase in the number of cells with decrease in size and increased glycogen deposition. The nuclei are at first relatively large, round, vesicular, then tend to become oval shaped and then appear as elongated rod-shaped pyknotic nuclei. The term "luteal cells" has been suggested for cells containing such nuclei, since they occur in moderate numbers during the luteal phase. Polymorphonuclear leucocytes are usually present during the early phases of pregnancy and tend to disappear soon after the twelfth week (Figs. 1 to 4). Not infrequently, however, smears with predominantly polymorphonuclear leucocytes are found also during the later stages of pregnancy, but are without significance as to the course of gestation. The characteristic changes of later pregnancy, consisting of very large clusters of small luteal cells with a high glycogen content (Fig. 4), may be frequently found also during the earlier stages. Vaginal smears are thus unreliable for the evaluation of the phase of pregnancy.

*Aided by a grant from Ayerst, McKenna and Harrison, Ltd., New York, N. Y.

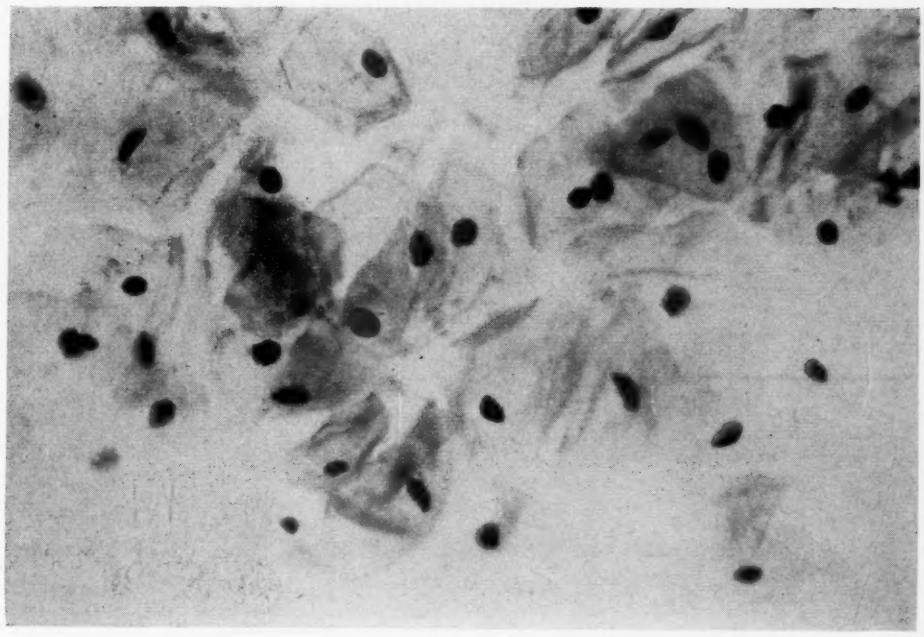

Fig. 1.—Early pregnancy. Accentuation of the luteal phase.

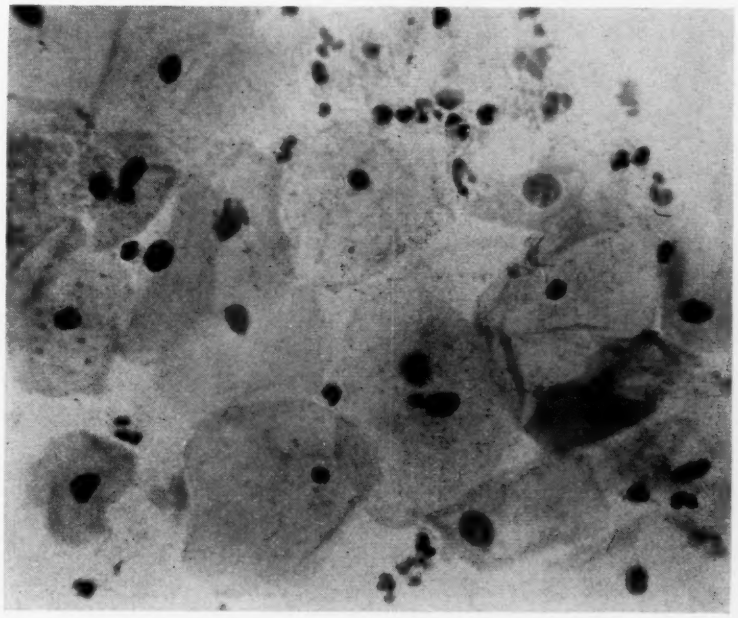

Fig. 2.—Tenth week of pregnancy. Note especially the large cells with large, round, vesicular nuclei. There are polymorphonuclear cells and small numbers of Döderlein bacilli.

Fig. 3.—Twentieth week of pregnancy. Note decreased cellular size with increased folding, elongation of nuclei, and absence of polymorphonuclear leucocytes.

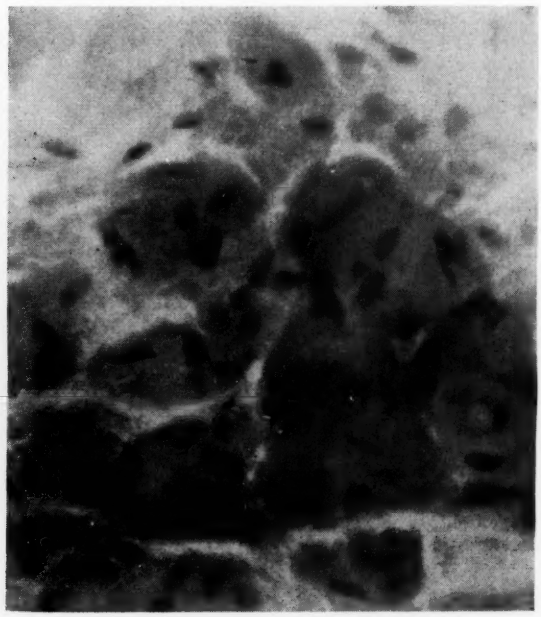

Fig. 4.—Thirty-sixth week of pregnancy. Note the increased number of cells of smaller size with increased number of rod-shaped nuclei of the so-called luteal cells.

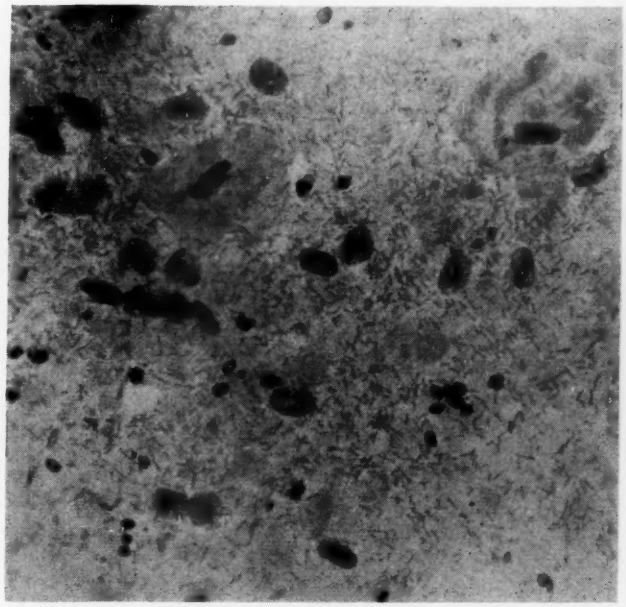

Fig. 5.—Cytolytic smear. Note the complete destruction of cellular cytoplasm. The nuclei are free and intact and there is a large number of Döderlein bacilli.

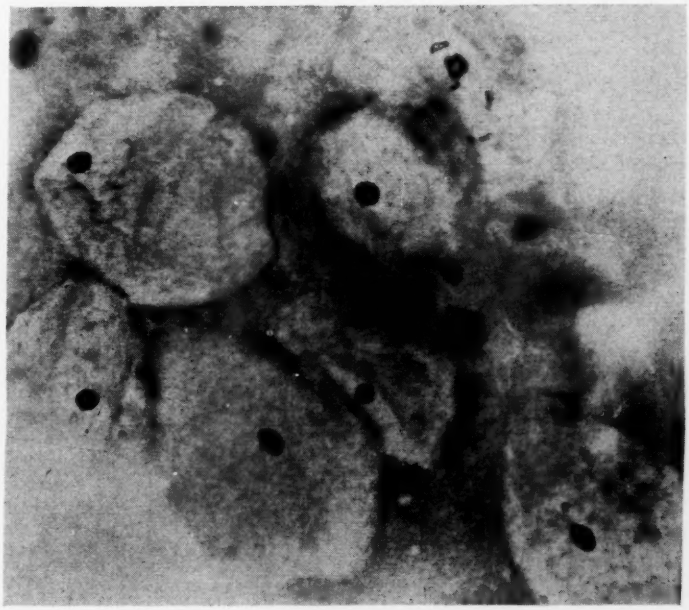

Fig. 6.—Mucoid cornified type of smear. Most cells are fully cornified. The dark substance surrounding and covering the cells is mucoid material.

In addition to these progressive changes, three specific types of smears are frequently encountered. Each of these presents features identical to those found in menstrual disturbances and other endocrine disorders.

The cytolytic smear is characterized by a large number of Döderlein bacilli with almost or complete destruction of cellular cytoplasm. The nuclei, usually relatively large, round, or oval and vesicular, are intact and there is usually evidence of increased estrogen activity, such as single cornified cells and free rod-shaped pyknotic nuclei of destroyed luteal cells (Fig. 5).

There are two types of androgenic smears. The mucoid cornified smear consists of fully cornified cells and abundant mucoid material. Döderlein bacilli or leucocytes are not found in association with this smear (Fig. 6). The glycolytic type is the other androgenic smear and shows extracellular glycogen with cellular glycopenia (Fig. 7).

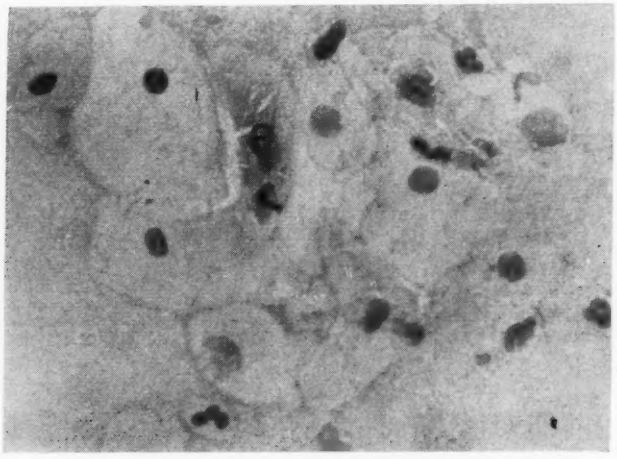

Fig. 7.—Glycolytic smear. There is cellular glycopenia with extracellular location of glycogen.

TABLE I. SPECIFIC ESTROGENIC AND ANDROGENIC SMEARS IN RELATION TO THE FETAL SEX

STAGE OF PREGNANCY (WEEKS)	TYPE OF SMEAR	SEX PREDICTED	SEX DELIVERED
16	C	Female	Female
18	C	Female	Female
18 and 24	C	Female	Male*
19	MC	Male	Male
19	EG	Male	Male
20	MC	Male	Male
22	C	Female	Female Twins
22	C	Female	Female
24	C	Female	Male*
24	C	Female	Male*
27	MC	Male	Male
27	C	Female	Female
28	MC	Male	Male
28	MC	Male	Male Twins
28	C	Female	Female
32	C	Female	Female

C—Cytolytic (estrogenic) MC—Mucoid cornified (androgenic) EG—Extracellular glycogen (androgenic) *—Error

The determination of the fetal sex was attempted only with such specific smears between the sixteenth and thirty-second week of pregnancy. In the presence of a cytolytic smear, a female fetus was diagnosed, while a male infant

was predicted on the basis of a mucoid cornified or glycolytic smear. Out of 86 normal pregnancies, specific spreads were obtained in only 22 women. At the time of writing this report, 16 have been delivered and, of these, the sex of the fetus was accurately predicted in 14, or 87 per cent (Table I).*

It is interesting to note that, in the case of female twins, the smear was markedly cytolytic, while the male twins were accompanied by a very intense mucoid cornified smear. The three errors occurred with the estrogenic smear.

In six cases, smears with an increased number of cornified cells without mucus were found and three patients aborted shortly after the appearance of this type of smear (Fig. 8).

It was found that pregnant women who show the typical late pregnancy changes in early phases of pregnancy (Fig. 4) are usually delivered of female infants. Seven women in this series showed between the sixteenth and twenty-fourth weeks advanced pregnancy changes and six, or 83 per cent, were delivered of female infants (Table II).

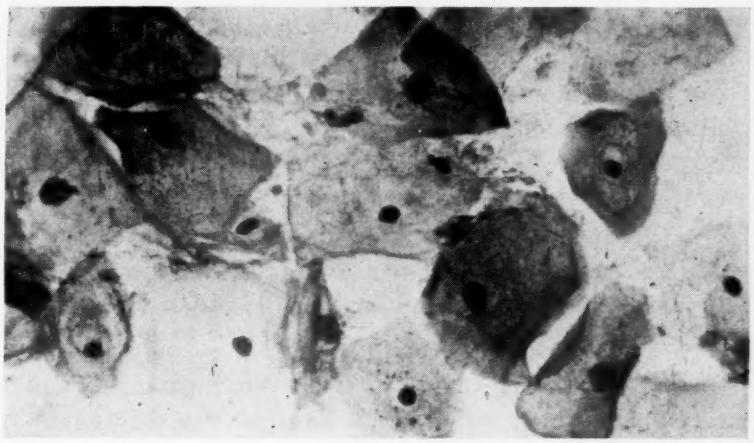

Fig. 8.—Most of the cells are cornified and there is no mucoid substance in this smear.

TABLE II. ADVANCED ESTROGENIC SMEARS IN RELATION TO THE FETAL SEX

STAGE OF PREGNANCY (WEEKS)	TYPE OF SMEAR	SEX PREDICTED	SEX DELIVERED
16	AE	Female	Female
19	AE	Female	Female
21	AE	Female	Female
21	AE	Female	Male*
23	AE	Female	Female
24	AE	Female	Female
24	AE	Female	Female

AE—Advanced estrogenic *—Error

Discussion

These data are in accordance with earlier findings in pregnancy.[7] The cytolytic smear was found in women on estrogen therapy and in conditions with a high estrogenic level.[6] Careful analysis of the smear itself shows evi-

*The six remaining women have since been delivered. There were three males and three females. Two errors occurred in respect to the cytolytic smear. This brings the relationship of specific smears to the fetal sex to an incidence of 81 per cent.

dence of estrogen activity. The Döderlein bacillus is viable only in an acid medium at a pH of 3.8 to 4.4, which apparently is due to a high estrogenic level.[8] During the menopause, when estrogen activity declines, the pH rises. The free rod-shaped nuclei of destroyed luteal cells, usually associated with cytolysis, are an additional sign of estrogen activity, since they occur, due to increased crowding of cells, in the presence of marked proliferation of the vaginal epithelium. Frequently, the presence of a number of intact cornified cells points to good estrogen production.

The androgenic, mucoid, cornified type of smear was found on androgen therapy and in conditions where a shift in the estrogen-androgen ratio had occurred toward an absolute or relative increase in androgens.[6] The combination of cornification with mucification is probably due to the fact that androgens inhibit the effect of progesterone on the vaginal epithelium, thus preventing the rapid desquamation of cells and thereby allowing the cells to mature to complete cornification under the effect of estrogen. The glycolytic smear is very rare. In a series of 253 pregnant women, it occurred in only eight and was in all cases associated with a male infant.[7] In about 2,500 nonpregnant women, it was seen in only four and was due to conditions of increased androgen activity. In the present series it occurred in only one woman and was followed by the birth of a male infant. The close relationship of such specific estrogenic and androgenic smears to the fetal sex is in accordance with earlier observations and supports the recent findings on the relationship of blood gonadotropins to the sex of the fetus.[9-11]

The extremely low incidence of specific smears during pregnancy limits the value of the vaginal smear method as a means for sex determination. The results, however, indicate that the maternal hormone levels change in accordance with the fetal sex. The source of the particular increased hormone is probably the fetus itself and the cases which either fail to show these specific changes or give errors may be explained by the fact that the maternal hormones may mask those of the fetus. It is interesting to note in this connection that all three errors occurred with estrogenic smears. Furthermore, the greatest percentage of specific smears is found between approximately the eighteenth and twenty-sixth weeks of pregnancy. After this, smears usually show the normal changes of advanced pregnancy. Gonadotropin assays during the eighteenth to twenty-sixth week of pregnancy have shown a greater percentage of specific reactions with a higher percentage of accurary.[11]

Five women showed smears consisting of polymorphonuclear leucocytes only and seven women presented smears with immature or basal cells.

The more definite outcome of this investigation is the knowledge gained on the normal changes and variations of vaginal smears during pregnancy. All types of smears can be found during normal pregnancy. The finding of increased cornification in three cases followed by abortion is interesting in this connection and confirms a previous report.[12]

Summary

The normal vaginal-smear changes during the course of pregnancy are presented. Increased cornification without mucification was encountered in only six cases. Three of these soon thereafter threatened to abort.

Specific estrogenic and androgenic smears are described and their significance and correlation to the fetal sex are discussed. The cytolytic smear consists of an increased number of Döderlein bacilli and complete destruction of cellular cytoplasm with intact nuclei and is believed to accompany high estrogen activity. This type of smear is associated with a female fetus. The mucoid cornified smear is the usual typical androgenic smear and is characterized by cornified cells with abundant mucoid material. The glycolytic type, with extracellular glycogen and intracellular glycopenia, is a very rare androgenic smear. Such smears are associated with a male fetus.

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FACTORS INFLUENCING SUCCESSFUL POSTERIOR PITUITARY TREATMENT OF FUNCTIONAL UTERINE DYSTOCIA WITH PARTICULAR CONSIDERATION OF ITS INTRAVENOUS ADMINISTRATION

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THE problem presented by the functional failure of uterine contractions in labor, i.e., uterine inertia, remains unsolved. The recognition of this difficulty is not new, for as early as 1807 Stearns[1] had written of the use of ergot in "lingering labor." However, with the great strides made in recent years in the treatment of puerperal infection, obstetric hemorrhage and cephalopelvic dystocia, uterine inertia, through its defiance of therapy, has gained in relative importance.

Posterior pituitary extract has been available to stimulate uterine contractions since 1909. Even Blair Bell, who introduced it, recognized that it was not a safe drug in the first or second stages of labor. The chief danger in his day and the succeeding decade was due to unreliable standardization and to the use of huge doses. These two factors put the use of the drug before the birth of the infant in disrepute, and after 1920 many articles appeared decrying its administration in the first and second stages. Teachers of obstetrics either forbade its use entirely or advocated modified methods of administration, such as the intranasal route,[2] which gave uneven and unpredictable absorption. These teachings prevented adequate and controlled evaluation of the drug, although physicians away from the shadow of teaching centers continued to employ it in increasing numbers. Even with the modern well-standardized product the dosage was usually too large and frequently mere clinical evaluation of the pelvis missed the less obvious types of cephalopelvic disproportion. This led to unfortunate and, too often, tragic results which still further discouraged any real investigation of the true merits of pituitary extract in the treatment of functional dystocia. However, recently two careful pituitrin studies have appeared from major clinics. Both Reid[3] and Eastman,[4] although cautious in their conclusions, feel that the stimulation of contractions in cases of inertia with pituitary extract is an efficacious and meritorious procedure. Their figures show a definite and real decrease in the incidence of difficult vaginal deliveries in such cases. They have both emphasized the necessity of extremely small dosages, given intramuscularly, not more often than every thirty minutes. Both authors stress the contraindications which pelvic contraction, elderly primiparity, and great multiparity offer. It is obvious from the results of these studies that even in indicated cases pituitary extract will solve only a portion of the problems. Even Blair Bell was aware of this, for in 1938 Jeffcoate[5] stated in the memorial lecture to his teacher that it was his cognizance of these occasional failures of pituitary stimulation that led him to urge the investigation of other drugs, such as estrogenic compounds in the treatment of uterine inertia.

While the infant mortality figures of both Reid and Eastman are better than could have been achieved in such cases by any other present-day method of treatment, excluding of course the radical use of cesarean section, neither gave any special attention to those instances in which pituitary extract therapy failed. It is only when investigation is particularly directed toward this point that the poor quality of fetal results becomes apparent. With this in view, much of the same material reviewed by Eastman was re-examined and transferred to special punch cards.

Present Study

The following is an analysis of 488 cases treated with posterior pituitary extract during the first and second stages of labor from Jan. 1, 1941, to Dec. 31, 1945, at the Johns Hopkins Hospital. Both pituitrin and pitocin were used at various times and, while a slightly better response was elicited with the former, the difference was not statistically significant. In the following tables no attempt is made to differentiate between the two. From 1941 to 1943 the initial dose was limited to one minim intramuscularly, and thereafter to ½ minim. Successive doses were never given more often than every thirty minutes, the injections sometimes being increased to 2 minims, depending upon the response. In no instance was a larger dose than 2 minims employed. All cases had clinically normal pelves, and in many this had been confirmed by x-ray pelvimetry. It is now mandatory in this clinic that the latter be taken prior to pituitary extract stimulation in every case to exclude unrecognized mid-pelvic contraction or asymmetry.

Table I groups the cases into successful, unsuccessful, and equivocal, in regard to the outcome of this specific type of therapy. These three terms are herein defined as follows: *Successful*—treatment with pituitary extract resulted in the full dilatation of the cervix and descent of the head to a level where an easy low forceps or spontaneous delivery was achieved. *Unsuccessful*—cases in which full dilatation of the cervix was not reached, or in which delivery had to be achieved by cesarean section or a difficult low or midforceps, or in which some other method of therapy in addition to pituitary extract was necessary. *Equivocal*—the use of pituitary extract in these cases was usually confined to one dose. Furthermore, in reviewing the cases, the essayist was not convinced

TABLE I. PITUITRIN STIMULATION. TOTAL FETAL MORTALITY IN INFANTS 1,000 GM. AND OVER DISTRIBUTED ACCORDING TO SUCCESSFUL, UNSUCCESSFUL AND EQUIVOCAL.

				CORRECTED*	
	DELIVERIES	DEATHS	MORTALITY	DEATHS	MORTALITY
Successful	354	16	4.5%	11	3.1%
Unsuccessful	47	10	21.2%	7	15.9%
Equivocal	87	2	2.3%	1	1.1 %

*Fetal heart not heard prior to pituitrin stimulation and congenital malformations incompatible with life omitted.

either by the length of the recorded delay in cervical dilatation or by the total length of labor that these were true cases of functional dystocia. The very low infant mortality rate in this group would seem to bear this out. The equivocal group will therefore be omitted from this analysis. The corrected and uncorrected fetal mortality in the various categories is also given in Table I. It is very striking that while the mortality rate in the successful group is close to the clinic average, there is a fivefold increase in the unsuccessful group.

Table II shows the distribution of cases by type of delivery and Tables III and IV by age and parity. These latter are definitely not factors influencing the outcome of this type of therapy. Most of the patients, but not all, were primiparas. Experience has taught that the treatment of highly parous or elderly individuals with antepartum pituitary stimulation is not wise. The only ruptured uterus in the series, reported in detail by Eastman, occurred in a 44-year-old para viii. Following this no pituitrin stimulation has been allowed in women of greater parity than iv.

TABLE II. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO TYPE OF DELIVERY

TYPE OF DELIVERY	SUCCESSFUL	UNSUCCESSFUL
Spontaneous	77	3
Low forceps, elective	102	3
Low forceps, indicated	151	12
Midforceps	0	3
Breech extraction	18	0
Willett forceps, successful	1*	2
Willett forceps, unsuccessful	3	1
Classical cesarean section	0	1
Low cervical cesarean section	0	5
Radical cesarean section	0	5
Extraperitoneal cesarean section	0	4
Twins	2	1
Low forceps, Dührssen incision	0	5
Midforceps, Dührssen incision	0	2
Total	354	47

*Pituitrin and Willett forceps begun simultaneously.

TABLE III. SUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION BY AGE AND PARITY

AGE	TOTAL	PARITY										
		0	i	ii	iii	iv	v	vi	vii	viii	ix	x+
< 20	61	56	5									
20-24	101	82	13	6								
25-29	85	64	15	4		2						
30-34	60	30	17	6	3	2	1				1	
35-39	38	18	8	4	2	2		1	1		2	
40+	9	2	1		1	1			1	2		1
Total	354	252	59	20	6	7	1	1	2	2	3	1

TABLE IV. UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION BY AGE AND PARITY

AGE	TOTAL	PARITY											
		0	i	ii	iii	iv	v	vi	vii	viii	ix	x+	UNKNOWN
< 20	10	9	1										
20-24	12	8	2	1	1								
25-29	8	7	1										
30-34	8	4	1		1					2			
35-39	5	4	1										
40+	4		1		1				1				1
Total	47	32	7	1	3				1	2			1

Tables V and VI deal with the time factor. Table V shows the distribution of cases according to successful and unsuccessful groups in relation to the duration of labor prior to the onset of treatment. In the analysis of these two groups the data were taken to be statistically different if the X^2 was 4 or

greater. The X^2 being 7.72, any difference in percentage is significant. Thus a greater percentage of unsuccessful cases labored thirty hours or more prior to the onset of treatment than in the successful group. Similarly in Table VI a greater percentage of the successful group completed their entire labors in less than thirty hours.

TABLE V. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO LENGTH OF LABOR PRIOR TO FIRST DOSE OF PITUITRIN

	CASES	LABOR LESS THAN 30 HOURS	LABOR MORE THAN 30 HOURS	PER CENT LABOR LESS THAN 30 HOURS
Successful	354	299	55	84.46
Unsuccessful	47	32	15	68.09
		$X^2 = 7.72$		

TABLE VI. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO THE TOTAL LENGTH OF LABOR

	CASES	LABOR LESS THAN 30 HOURS	LABOR 30 HOURS OR MORE	PER CENT LESS THAN 30 HOURS
Successful	354	266	88	75.14
Unsuccessful	47	19	28	59.57
		$X^2 = 5.14$		

Table VII shows the station of the fetal head in both groups prior to the onset of therapy. This apparently was a factor of prime importance in the outcome of the therapy, for in 23.4 per cent of the unsuccessful cases the head was higher than two fingerbreadths above the spines, while in only 6.78 per cent of the successful cases was this true. This is, of course, a highly significant difference.

TABLE VII. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO THE STATION OF THE FETAL HEAD

	CASES	HEAD 2 FINGERS OR MORE ABOVE SPINES	HEAD LESS THAN 2 FINGERS ABOVE SPINES	PER CENT WITH HEAD 2 FINGERS OR MORE ABOVE SPINES
Successful	354	24	330	6.78
Unsuccessful	47	24	36	23.40
		$X^2 = 14.39$		

In contrast to the station of the head, the dilatation of the cervix at the onset of therapy did not seem to play an essential role in the outcome, as shown by Table VIII.

TABLE VIII. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO DILATATION OF THE CERVIX

	CASES	4 CM. OR MORE DILATED	LESS THAN 4 CM. DILATED	PER CENT 4 CM. OR MORE DILATED
Successful	354	265	89	74.86
Unsuccessful	47	30	17	63.83
		$X^2 = 2.60$		

For the past year all women in labor more than twenty-four hours have been given prophylactic penicillin. Prior to this and during the entire period of this study, such was not the case. Whether this has much influence on the occurrence of intrapartum fever remains to be seen. However, in the cases tabulated in Table IX, the occurrence during labor of an elevation of 100.4° F. by mouth or greater was a very important factor in determining the successful outcome of pituitary stimulation.

TABLE IX. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO INTRAPARTUM FEVER

	CASES	FEBRILE	AFEBRILE	PER CENT FEBRILE
Successful	354	46	308	12.99
Unsuccessful	47	15	32	31.91
		$X^2 = 10.87$		

The clinical impression gained credence that cases of functional dystocia under pituitrin therapy did better with some form of pain relief. Various types of regional and general analgesia were tried but, as shown in Table X, the clinical impression remains unproved.

TABLE X. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO ANALGESIA

	CASES	ANALGESIA	NO ANALGESIA	PER CENT ANALGESIA
Successful	333	250	83	70.6
Unsuccessful	46	29	17	61.7
		$X^2 = 3.59$		

In an effort to overcome certain very obvious objections to the intermittent method of pituitary extract stimulation, the use of highly dilute continuous intravenous therapy was resorted to. Pituitrin was mixed with either normal saline or 5 per cent glucose in concentrations of 0.5 minim per 50 cubic centimeter. This mixture is given intravenously at the rate of 50 c.c. for the first half hour and 100 c.c. per half hour thereafter. There was a very gradual and physiologic increase in uterine contractions which were maintained only so long as the solution continued to run, and ceased with the cessation of the treatment. Patterns of uterine contraction under this form of stimulation have been studied with the Reynolds tokodynamometer and will be reported in detail later. It is sufficient to say here that this appears to be a much more physiologic method of pituitrin uterine stimulation. Table XI is similar to Table I and shows the distribution of cases of functional dystocia treated by the continuous method. They are distributed according to the success of the therapy and the fetal mortality rates calculated. The failure rate is approximately the same with this technique as with the intermittent method. There were no infant deaths, but this is perhaps a sampling error due to the small number of labors treated.

TABLE XI. INTRAVENOUS PITUITRIN STIMULATION. TOTAL FETAL MORTALITY INFANTS 1,000 GRAMS AND OVER DISTRIBUTED ACCORDING TO SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION

	DELIVERIES	DEATHS	MORTALITY
Successful	36	0	0
Unsuccessful	7	0	0

Conclusions

1. In 401 cases of functional uterine dystocia treated with intermittent small intramuscular doses of pituitary extract, failure to achieve easy delivery occurred in 11.7 per cent.

2. Factors contributing to the failure of this form of therapy were: (a) long duration of labor; (b) long duration of labor prior to treatment; (c) intrapartum fever; (d) high station of head when treatment was first instituted.

3. Factors playing no part in the failure of this form of therapy were: (a) the extent of dilatation of the cervix at onset of therapy; (b) analgesia.

4. Continuous intravenous injection of posterior pituitary extract while apparently a more physiologic form of therapy, did not increase the success rate.

5. The excellent fetal results in both successful and unsuccessful groups of intravenously stimulated patients are encouraging, but might not be confirmed in a larger series.

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THE SIGNIFICANCE OF ABNORMAL MENOPAUSAL VAGINAL SMEARS

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NATIONWIDE publicity in the past year has brought many women to our Cancer Prevention and Detection Center for routine physical examination "check-up." Up to the present time, we have examined vaginal smears in approximately 900 women who had no specific complaints. Of these 42 per cent were within or beyond the menopausal age group. The smears in these patients fell into one of two types: the "crowded menopausal," seen chiefly in women at the onset of the menopausal syndrome; and the "atrophic menopausal," evident in women well within their menopause. Twelve out of a total of 378 cases, 3.16 per cent of these smears, presented a disturbing picture because of the marked resemblance that these particular smears bore to cases of proved cancer.

It has been apparent for some time that cancer cells grow for indeterminate periods before a tumor can be grossly recognized. True carcinoma of the cervix, particularly, can remain unnoticed for long periods of time notwithstanding regular pelvic examinations. On many occasions when cancer of the cervix is eventually recognized, careful review of previous biopsy specimens reveals previously unnoticed abnormalities.

Taylor and Guyer[1] recently reported a case in which a patient had been followed for a seven-year period for chronic cervicitis and cervical erosion, with repeated negative cervical biopsies. At the end of seven years, biopsy revealed a definite squamous-cell carcinoma of the cervix. When other sections were made of the original block of tissue, several slides showed small tongues of abnormal squamous cells extending into the fibrous stroma.

In 1945, Rubin[2] reported three early cervical carcinomas in three clinically unsuspected cases incidental to operations for plastic surgery.

TeLinde and Galvin[3] also stress the fact that carcinoma of the cervix may be unrecognizable by clinical examination or even routine biopsy. Their finding of eight definitely cancerous lesions in normal or almost normal-looking cervices in one year is rather startling. In none of these cases was a diagnosis of cancer possible from palpation or inspection of the cervix. In approximately half the cases, several well-trained gynecologic pathologists were unwilling to make a diagnosis of carcinoma from the changes noted in the biopsy specimens. In 90 per cent of the cases, the authors found, after removal of the cervix, absolute evidence of invasive carcinoma.

In all of the quoted references, no mention is made of routine vaginal smears. The smear technique has been criticized to a certain degree, because of the time involved in studying slides. It has been further claimed that the

examination of the slide is a tedious, lengthy procedure and it is very possible to miss an abnormal cluster of cells in the smear. In our experience, we have not found it too difficult to detect an abnormal slide. With a sound training in interpreting normal cytology, a glance at an abnormal smear strikes one immediately in many cases. In such instances, a minute and lengthy examination follows.

The outstanding error which would discredit the value of these smears or the value of this "screening" method as developed by Papanicolaou, would be to entrust this work to inadequately trained technicians. The average well-trained technician should be able to aid the pathologist or cytologist by sorting the slides, but no clinic can expect to train a technician for one or two months and then entrust that technician with making diagnoses. An already well-trained pathologist or cytologist must spend ample time learning first the characteristics of normal vaginal smears and their interpretation and then become thoroughly familiarized with the abnormal cells.

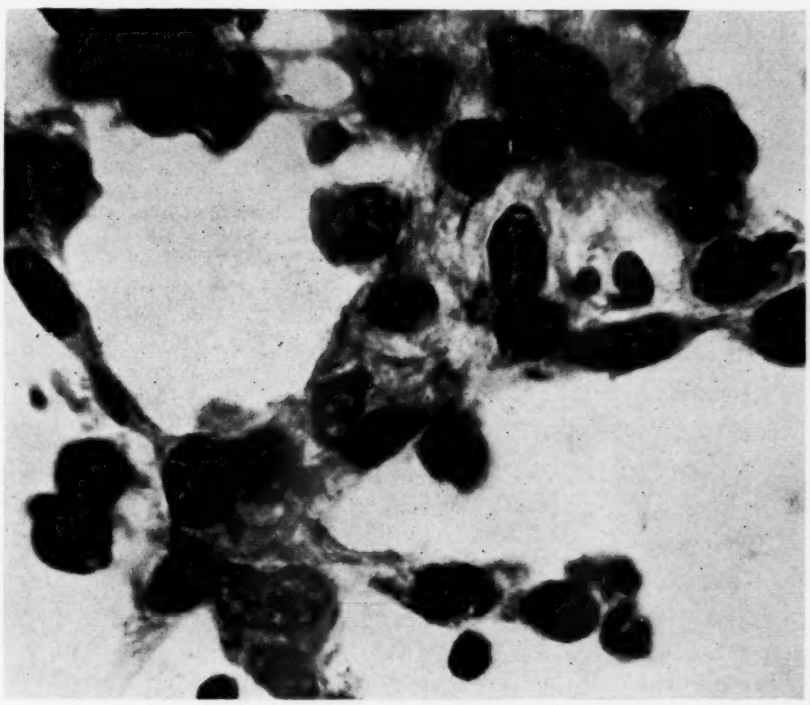

Fig. 1.—Abnormal menopausal smear. Cells show variations in size, shape, staining reaction and density of the nuclear chromatin. These cells have some of the features of malignant cells but are non-cancerous. (Confirmed by repeated smears and multiple biopsies).

Perhaps examination of routine smears on these so-called normal-looking cervices, described by TeLinde and Galvin, could have afforded some inkling of suspicion. The shedding exfoliative characteristics of genital tract malignancies are manifested prior to clinical signs or symptoms. Corroboration of the success and utility of this method has been amply provided by Papanicolaou and Traut,[4] Meigs,[5] Ayre,[6] Jones, Neustaedter, and MacKenzie.[7]

All of these instances of delayed cancer diagnosis indicate that carcinoma can exist without clinical signs and/or symptoms of malignancy, and is even unrecognizable by histologic study. The knowledge of the above has made us

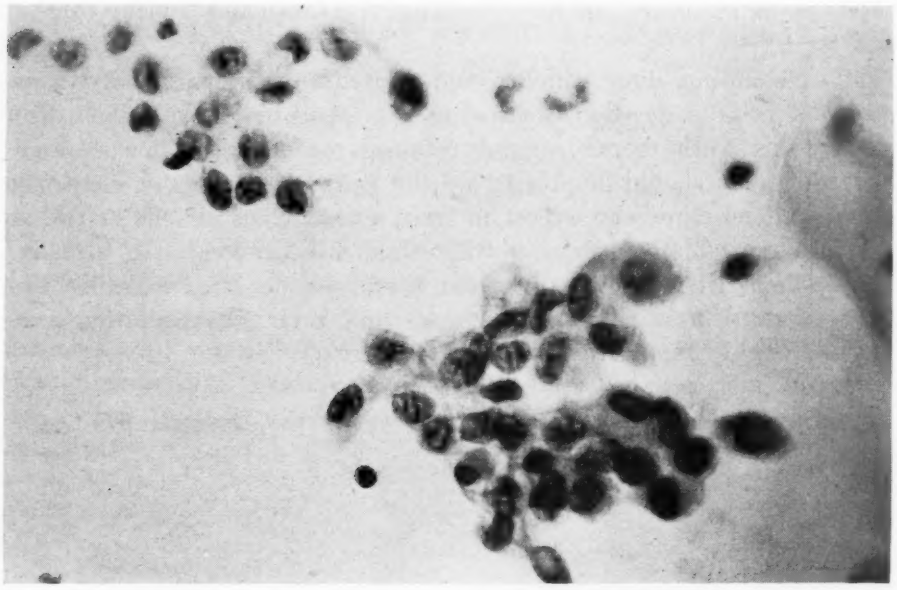

Fig. 2.—Atrophic menopausal smear showing atypical cellular changes.

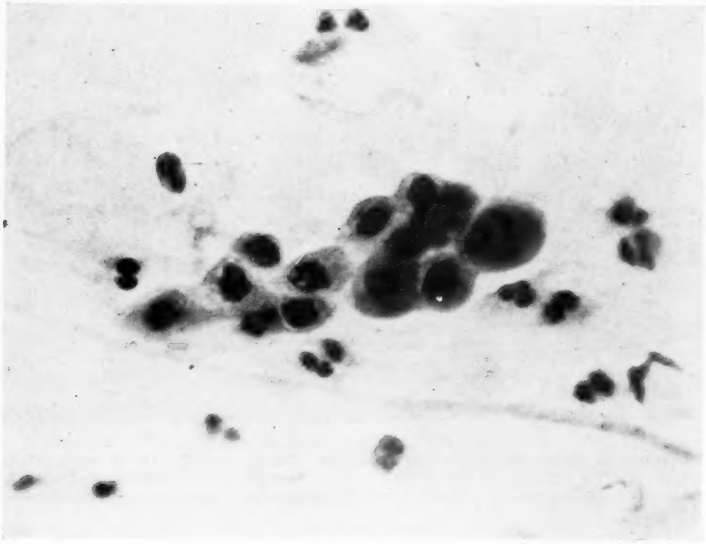

Fig. 3.—Cluster of basal cells from atrophic menopausal smear. Note the anisocytosis, anisonucleosis and nuclear hyperchromatism.

very wary in interpreting certain types of smears in our Center. Our uncertainty is particularly pointed in the case of certain types of menopausal smears.

In examining the disturbing menopausal smears, repeated and numerous biopsies failed to reveal any definite evidence of carcinoma. In the photographs, the abnormal cytology is very apparent. The cells in the photographs

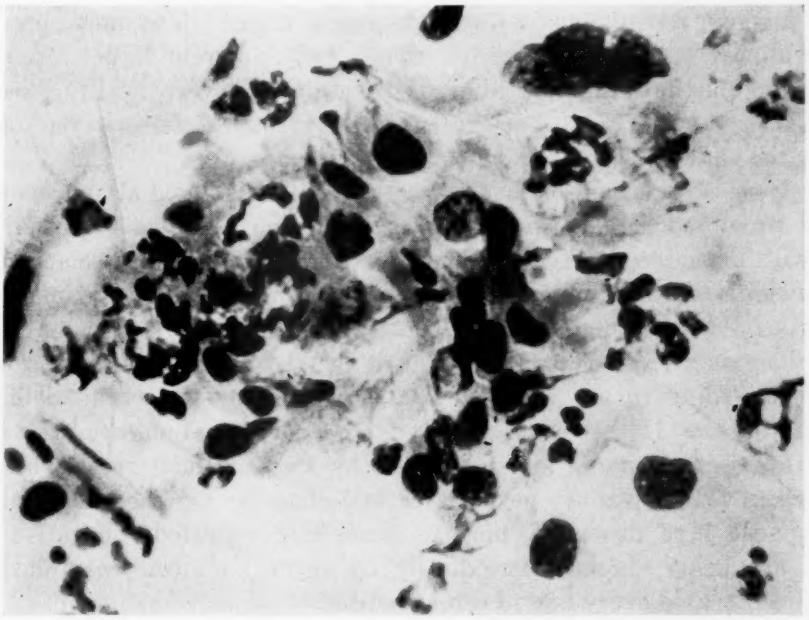

Fig. 4.—This smear is a proved case* of squamous-cell cancer of the cervix. Note the similarity in the cells in this smear and that of Fig. 1.

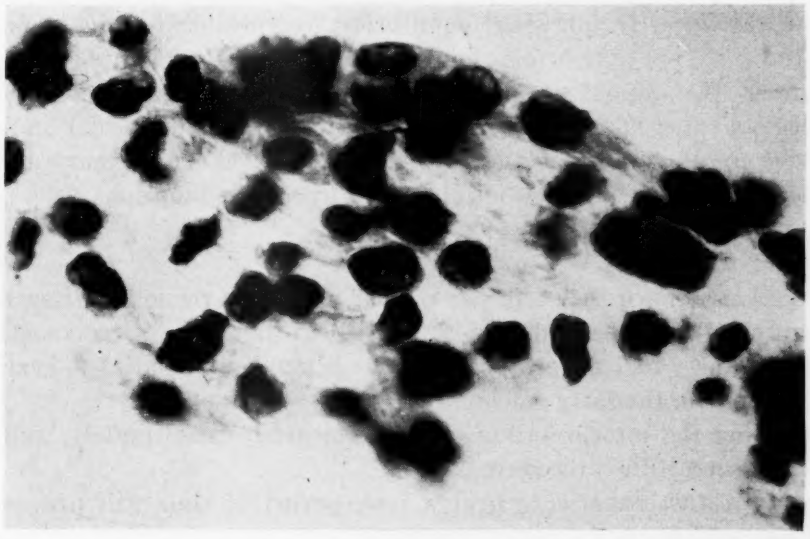

Fig. 5.—Squamous-cell cancer of the cervix.* Note the more marked anisonucleosis, anisocytosis, and nuclear hyperchromatism.

evidence a great variety of size and form. The cells in many instances tend to form dense groups with considerable overcrowding and overlapping. Some are relatively small and have comparatively large nuclei in relation to the size

*Confirmed by biopsy.

of the cells. In some, vacuolization of the cytoplasm is clearly evident. The nuclei are bizarre in shape and in instances, hyperchromatic. Nucleoli are occasionally conspicuous. Elongation of the cells is a frequent occurrence. The cells sometimes become so long that they have lost their epithelioid form and acquire a close resemblance to smooth-muscle fibers. The most pronounced changes appear to be in the nuclei. They are relatively large, eccentric, indented, irregular in outline, bulge in all directions, and occasionally show hyperchromatism. Such cellular patterns ordinarily satisfy the criteria for malignancy in the vaginal smear.

Of all the 378 smears of menopausal patients examined at the Center, 3.16 per cent presented an abnormal pattern. Since our interest is primarily concerned with detection of early cancer prior to apparent clinical manifestations, we adopted the Papanicolaou classification of abnormal cells and malignancies in order to avoid missing very early cancer, and to study the significance of abnormal cytology, particularly in lieu of negative biopsy findings for malignancy. According to the Papanicolaou classification,* these can definitely be classified as Class III; they look very much like typical smears of carcinoma. Extensive studies in large series of cases by Papanicolaou reveal that 50 per cent of Class III smears are positive for malignancy. On the abnormal smears of menopause here discussed, biopsies have been repeatedly negative. These patients are being checked periodically by careful clinical examination, and smears are repeated every two to three months.

Are these cases of latent carcinoma? Are they potential malignancies for future diagnosis? Will repeated follow-up make a diagnosis of malignancy at a future date? Or are they just peculiar smears, seen during menopause? Are certain disturbances in hormonal equilibrium responsible for the peculiar picture? And if so, are they benign findings with no apparent significance? If the latter is true, the vaginal smear should be used with great discretion, and only by cytologists experienced in the diagnosis of cervical and fundal malignancy. This would eliminate a great number of false positives, unnecessary alarm, and unnecessary operative intervention in spite of negative biopsies.

Summary

1. We have shown that 3.16 per cent of all smears made in 378 menopausal patients present an abnormal pattern similar to that seen in carcinoma.

2. We believe that an intensive follow-up study is essential to evaluate the smear technique in the early detection of female genital cancer.

3. Leaving the interpretation of these smears to inadequately trained personnel will discredit the procedure.

4. Only a vast experience over a long period of time will prove whether or not these smears are merely misleadingly suspicious, or are really very early indications of a carcinoma which will be proved by standard and recognized methods at a much later date.

*Papanicolaou Classification:
Class I. Absence of abnormal or atypical cells.
Class II. Atypical cells present but without abnormal features.
Class III. Cells with abnormal features but not sufficiently pathognomonic.
Class IV. Fair number of pathognomonic cells and cell clusters.
Class V. Large number of conclusive cells and cell clusters.

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NONINVASIVE CERVICAL CARCINOMA

Clinical Features*

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PEMBERTON and Van S. Smith introduced the concept of noninvasive carcinoma or anaplasia of the cervical epithelium nineteen years ago, but pathologists in particular were unimpressed. Three years later Schiller of Vienna presented data on noninvasive cervical carcinoma before the New England Pathological Society.[12] Nevertheless, there is still not general acceptance of the idea that noninvasive anaplasia of the cervix is a malignant process. Anaplasia is defined to include collectively loss of cellular polarity and increased hyperchromaticity, hypertrophy, and variation in shape of the nucleus. Many believe these characteristics are sufficient to warrant a diagnosis of malignancy.[1, 3, 4, 5, 7, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 24, 25] Whether or not the basement membrane is penetrated is immaterial to the fundamental nature of the epithelial growth, and merely determines the presence or absence of invasive qualities. Thus, penetration of the basement membrane is only a criterion of invasion and not of malignancy, while absence of it does not imply benignancy.

No one knows how long a noninvasive carcinoma remains localized before becoming invasive. Graves,[9] as do others[14, 24] estimate the time interval to be at least ten to twelve years. Most noninvasive lesions have been discovered by chance following incidental operation on the cervix. Recently, several were detected with cytologic methods.[7, 15, 19] This report concerns seventeen women with noninvasive cervical carcinoma studied by cytologic methods and biopsy. Several of these were followed for a number of years.

Procedure

The diagnosis of noninvasive carcinoma of the cervix was seldom made at Parkland Hospital prior to 1946. Instead, it was usually reported as "anaplasia" or "hyperplasia." Cytologic methods instituted during 1946 for the detection of early cancer caused us to review all the records pertaining to hyperplasia and anaplasia of the cervix back to Dec. 31, 1935. Between that date and Jan. 1, 1946, ten specimens were found which on review were interpreted as noninvasive carcinoma. Seven other new cases were detected between Jan. 1, 1946, and Nov. 1, 1947.

The cervical smear and scraping or vaginal smear were used to study most of the patients. The vaginal smear was employed if the cervix was not present. Most of the women with a uterus had a cervical biopsy for serial sectioning and study, and then a total hysterectomy.

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Incidence

A philosophy of cancer consciousness was introduced at Parkland Hospital with the formation of the present Department of Obstetrics and Gynecology in January, 1944. Eventually more careful pelvic examinations with visualization of the cervix were done and better records made. Previous to Jan. 1, 1944, subtotal hysterectomy was done. After that date total hysterectomy became the procedure of choice. Early in 1946 cervical and vaginal smears were employed in selected cases. Later in the year multiple, rather than single, samples were taken from tissues to be examined microscopically. Almost as many noninvasive carcinomas of the cervix were discovered in the last twenty months (seven cases) of the period of study as were found in the preceding ten years (ten cases). During this period of time, the clinic population remained relatively stable.

Age of Patient

The average age of patients with noninvasive carcinoma was 36.2 years, as contrasted to 43.5 years for women with frankly invasive carcinoma treated in the same clinic. One in three of those with noninvasive lesions was under 30 years old, while the corresponding figures for those with invasive cervical carcinoma were one in thirty-eight.

Signs and Symptoms

The usual signs of cervical carcinoma, as vaginal bleeding or leucorrhea, were seldom present. The cervices of nearly one-third of the women with noninvasive lesions originally appeared normal, while those of the remaining number were "eroded," or the description was unavailable. Subsequently, one-third of the erosions disappeared. In other words, over one-half (ten) of the cervices were grossly normal sometime during the period of observation. Seven patients had no symptoms referable to the genital tract between the time of the first biopsy and the follow-up study.

Results

Collected data for the 17 women with noninvasive carcinoma are given in Table I. For the purpose of discussion they are considered in three categories. The first included four patients untraced, died of causes other than cancer, refused complete examination, or contacted only by letter. The second group contained six patients seen nineteen months to six years after the original biopsy was taken. Two, treated by cervical amputation, were well six years later. Three still had noninvasive carcinoma, while the sixth showed no evidence of atypical cervical growth. The third group was composed of the seven women with noninvasive carcinoma seen during the last twenty-month period of this study.

In every instance where anaplastic epithelial cells were found in the cytologic smear, anaplasia of the cervical epithelium was noted in the biopsy.

Comment

The day has passed when anaplastic epithelium can be considered noncancerous,[4] or at the most only precancerous, because it is confined by the basement membrane. Apparently the life of a cervical cancer covers a period of many years during which there may be a long irritative stage of cervicitis and a shorter period of clinical latency.[9] There are, at least, three reasons why some pathologists are loathe to agree that anaplasia without invasion is a form of cancer. First is the paucity of patients with noninvasive carcinoma followed until they developed invasive carcinoma. Reports of only fifteen such were

TABLE I. NONINVASIVE CERVICAL CARCINOMA

PATIENTS	AGE	APPEARANCE OF CERVIX	DATE SEEN	PROCEDURE	HISTOLOGIC DIAGNOSIS	REMARKS
1	38	Normal	July, 1938	Autopsy	Noninvasive carcinoma	Died of nephritis
2	22	Eroded	4/13/39	Biopsy	Noninvasive carcinoma	Untraced
3	29	Mild erosion	7/27/40	Subtotal hysterectomy and cauterization cervix	Noninvasive carcinoma	Untraced
4	33	Eroded	4/25/41			
	34	granular	6/26/42	Cervical biopsy	Noninvasive carcinoma	
	36	Leucoplakia	12/20/44			
	37	Eroded	11/ 5/45			
	39	Normal	8/24/47	Cervical scraping	Anaplastic epithelial cells	
			8/25/47	Cervical biopsy	Noninvasive carcinoma	
			8/28/47	Hysterectomy	Noninvasive carcinoma	Followed 6½ yrs.
5	39	Eroded	10/ 1/41	Subtotal hysterectomy and cauterization cervix	Noninvasive carcinoma	
	45	Normal	10/21/47	Cervical smear	Normal	Followed 6 yrs.
6	47		8/25/41	Cervical biopsy	Cervicitis	
		Normal	11/ 6/41	Total hysterectomy	Noninvasive carcinoma	
	53		Aug., 1947	Vaginal smear	Normal	Followed 6 yrs.
7	52	No data	7/ 9/43	Cervical biopsy	Noninvasive carcinoma	
	55	Normal	4/15/47	Amputation cervix	Noninvasive carcinoma	Followed 3¾ yrs.
8	24	No data	10/25/43	Cervical biopsy	Noninvasive carcinoma	
	25	No data	7/25/44			Normal delivery
	27	Normal	6/ 1/46			
	28	Normal	9/23/47	Cervical smear	Normal	
			11/10/47	Cervical smear	Normal	
			11/11/47	Total hysterectomy	Normal	Followed 4 yrs.
9	31	Eroded	8/ 8/44	Cervical biopsy	Noninvasive carcinoma	
	34	Normal	4/28/47			Followed 2 yrs.
10	22	Polyp	9/27/45	Cervical biopsy	Noninvasive carcinoma	
	24		Sept., 1947			By letter found to be living and well
11	37	Eroded	2/21/46	Cervical biopsy	Noninvasive carcinoma	
		Normal	8/31/46			
	38	Small erosion	9/25/47	Cervical smear	Anaplastic epithelial cells	
			10/ 7/47	Cervical biopsy	Noninvasive carcinoma	
			11/12/47	Cervical smear	Anaplastic epithelial cells	
			11/13/47	Total hysterectomy	Noninvasive carcinoma	Followed 17/12 yrs.

TABLE I—CONT'D

PATIENTS	AGE	APPEARANCE OF CERVIX	DATE SEEN	PROCEDURE	HISTOLOGIC DIAGNOSIS	REMARKS
12	45	Erosion	3/30/46	Cervical biopsy	Noninvasive carcinoma	
			4/11/46	Total hysterectomy	Noninvasive carcinoma	
			10/27/47	Vaginal smear	Normal	Followed 17½ yrs.
13	60	Normal	4/ 1/47	Cervical smear	Anaplastic epithelial cells	
			6/ 6/47	Biopsy	Noninvasive carcinoma	Refused further treatment
14	37	Normal	4/15/47	Total hysterectomy	Noninvasive carcinoma	Chronic pelvic inflammatory disease
15	26	Eroded	July, 1947	Total hysterectomy	Noninvasive carcinoma	Chronic pelvic inflammatory disease
16	35	Normal	4/24/47	Total hysterectomy	Noninvasive carcinoma	Chronic pelvic Inflammatory disease
17	28	Granular	10/24/47	Cervical smear	Anaplastic epithelial cells	
			10/25/47	Biopsy	Noninvasive carcinoma	
			11/ 6/47	Hysterectomy	Noninvasive carcinoma	

found.[8, 11, 16, 18, 20, 21, 23, 25] Apparently all these observations were made by hindsight. One of these women remained well for nearly twenty years, but ultimately developed clinically invasive carcinoma. Second, in a few instances, the patient remained healthy. Perhaps all of the anaplastic lesion was excised in the first biopsy, the patient died of some other disease before clinical cancer appeared, or the original histologic interpretation was incorrect. Finally, there are those who do not consider a lesion as cancer until invasive properties are demonstrable.[20] This is a matter of definition of the word "cancer." Such a position immediately and surely prevents study of early cancer by refusal to accept the possibility that cancer cells may have an infancy and an adolescence. It would *appear desirable to define "cancer" according to cell morphology* rather than the stage to which growth has progressed, since specific chemical and morphologic properties of malignant tumor cells are now known to exist and can be recognized. This attitude is essential if we ever hope to make the earliest recognition of cervical carcinoma.

Replacement of the epithelium in the cervical glands by downgrowth of anaplastic surface epithelium has been regarded by some observers as evidence of early invasion. But there is reason to believe that invasion of a gland does not have the same importance as frank penetration of the basement membrane. Patient 4 presented evidence of extension into the cervical glands over a six-year period illustrating these changes may remain latent for several years and behave as a malignancy limited to the surface. It is known that different types of fully established tumors have a different capacity to grow and destroy. Therefore, it is reasonable to assume that a developing cancer does not grow with the same momentum as does a fully established tumor.[22]

The average age of women with frankly invasive cervical carcinoma is 46 years.[6, 14] On the other hand, the average age for noninvasive cervical carcinoma was 41 years, as determined by a combined analysis of 147 patients from our own material and that of others.[11, 13, 14, 15, 18, 19, 20, 21, 23, 25] Pund and Auerbach,[14] by studying consecutive cervical specimens examined in their clinic, found the average age was 36.6 years. The age differences indicate that it takes several years for cervical carcinoma to become recognizable clinically and that the noninvasive lesion is found relatively early in life compared to overt invasive carcinoma.

It would be interesting to know how early noninvasive carcinoma actually begins. From the standpoint of treatment, this fact is extremely important. Here, if ever, is the *ideal time to cure cancer*. Noninvasive carcinoma can be treated with a low operative mortality and few sequelae, while the treatment of frankly invasive carcinoma carries a high mortality from the disease alone and a comparatively high incidence of sequelae to treatment used.

Finally, we are of the opinion, as are others,[2, 7, 19] that the cytologic smear is a valuable adjunct in detecting the presence or absence of noninvasive cervical carcinoma.

Summary

Of 17 women with noninvasive carcinoma, over a third were under 30 years old. Several of the patients had a normal appearing cervix and presented no symptoms referable to the genital tract. In two instances the carcinoma remained localized over six years. Cytologic methods were a reliable adjunct to biopsy in detecting the presence of the noninvasive cervical carcinoma.

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INFECTIOUS MONONUCLEOSIS COMPLICATING PREGNANCY WITH FATAL CONGENITAL ANOMALY OF INFANT

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IN RECENT years, maternal rubella in the first trimester of pregnancy has been shown to be closely associated with high incidence of congenital anomalies in the offspring, and, at the present time, various other virus diseases are under suspicion. Infectious mononucleosis is generally considered a virus infection, although there is no conclusive evidence to support this contention. Its incidence in the general population is unknown because the diagnosis is frequently not made and because it is not usually a reportable disease. Therefore, we are reporting the coincidence of conception and infectious mononucleosis, with results disastrous for the fetus.

Mrs. R. K., a 27-year-old nulligravida, consulted one of the authors for the first time on May 20, 1946, complaining of vaginal discharge which had been present since the onset of the menses, and of general malaise for one month. Discharge was continuously present, rather thick, colorless, and odorless, and troubling her by causing chafing of the thighs. All sorts of douches had been tried without success. Catamenia began at 11 years of age, every 28 days, for four days. Several periods at fifteen-day intervals a few years previously had caused a physician to suspect miscarriage, but this was never confirmed. Last menstrual period May 14, 1946.

For the preceding month she had felt poorly, with arthralgia in fingers and knees, poor appetite, and restless sleep. For ten days prior to the first visit she had a daily afternoon chill, with temperature to 100.6° F. Since May 18, 1946 there had been mild sore throat. In the preceding week she had lost six pounds.

Past history, family history, and review of systems were essentially noncontributory.

Physical examination revealed a small woman, 4 feet 10 inches in height and weighing 116 pounds, who appeared tired but not particularly ill. Temperature 98.2° F., blood pressure 110/60. The only positive physical findings at this time were limited to the tonsils, which were both large, juicy, and rather dusky in appearance, with a small ulcer and many plugs of exudate on the right. The ulcer was covered by a gray adherent membrane. No lymph node enlargement was evident. Pelvic examination was completely negative.

Laboratory Findings.—Red blood count 4.89 millions, hemoglobin 14 Gm., white blood count 15,150. *Smear:* Polymorphonuclear leucocytes 22 (nonsegmented 14), lymphocytes 70, large mononuclears 6, questionable myelocytes 2. Many of the lymphocytes were suggestive of infectious mononucleosis. *Urine:* Yellow, acid, specific gravity 1.015; sugar, albumin, and sediment negative. Smear of tonsillar ulcer showed a few fusiform bacilli.

At this time, a diagnosis of either Vincent's angina or infectious mononucleosis was considered. It was believed that the vaginal discharge was not abnormal in amount or type but caused irritation because of plump thighs and profuse perspiration. She was given penicillin-beeswax, 300,000 units intramuscularly. The next day her throat looked worse and a second blood smear appeared typical of infectious mononucleosis, and blood taken at the previous visit was reported as showing a heterophile antibody titer of 1:640. Previously taken throat cultures and Mazzini flocculation were negative. She was followed during the next two months and gradually recovered. Meanwhile she failed to menstruate. Pelvic examination on

June 24, 1946, showed no change, and it was not until July 24, 1946, after the patient had missed two periods, that the diagnosis of pregnancy could be established by examination. Probable estimated date of confinement Feb. 25, 1947.

Prenatal course was uneventful. Total weight gain was 12½ pounds. No blood pressure elevation, urine was negative throughout. X-ray pelvimetry on January 22 revealed a breech presentation left sacroanterior and the following measurements: inlet anteroposterior 9.75 cm., transverse 12.25 cm., interspinous 10 cm., outlet intertuberous 9 cm., posterior sagittal 5.5 cm. In view of the presentation and small pelvis, cesarean section was thought advisable. On March 5, 1947, she was admitted to the hospital for elective section. On the same night, she fell into labor spontaneously, and section was performed after 3 hours. The male infant weighed 5¾ pounds and had good muscle tone. He breathed and cried spontaneously. About twelve hours after birth, he began to have respiratory distress with occasional apnea. Cyanosis was present, but not marked. Twenty-four hours after birth a systolic murmur was heard over the precordium. X-ray showed an enlarged heart. In spite of constant oxygen and other supportive measures, he died forty-eight hours after birth.

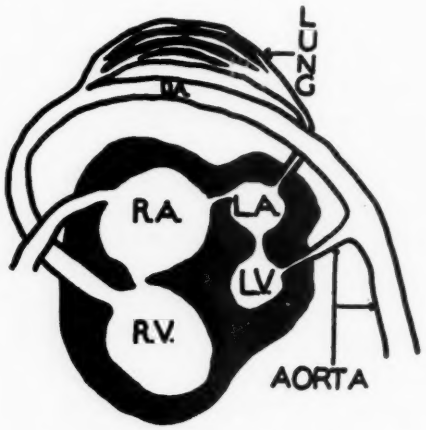

Fig. 1.—Diagram of heart, roughly representing the anatomical relations and relative size of the heart chambers and great vessels. R.A. = right auricle. R.V., L.A., and L.V. = succeeding chambers. D.A. = ductus arteriosus.

At post-mortem (Willimantic Autopsy No. 45), there was seen an externally normal male infant. A complete examination, excepting eyes, showed changes only in the heart and great vessels. The essential finding was a marked hypoplasia of the left auricle, left ventricle, and aorta in a 15 Gm. heart. Right chambers were relatively and absolutely hypertrophied, showing between 5 and 6 times the dimensions and capacity of those on the left (Fig. 1). Arrangement and sequence of great vessels, valves, and chambers were normal, as were their anatomical relations. Valve circumferences were, tricuspid 32 mm., pulmonic 23 mm., mitral 10 mm., and aortic 8 mm. The aorta was 3 mm. in diameter at the base of the heart and 5 mm. at its junction with the 6 mm. ductus arteriosus. The interventricular septum was intact, and the foramen ovale persisted as an oblique communication 1 mm. in diameter and 3 mm. in length. It was anatomically patent and functionally closed.

The endocardium of the left ventricle, and, to a less degree, that of the left auricle, showed a gray-white thickening which obliterated or flattened trabeculae and papillary muscles. In the structure first named, the process was 1 mm. thick in many sites, and obliterated the normal transparency of the endocardium. Microscopically, the process was one of fibrosis with varying degrees of cellularity and hyaline change (Fig. 2). Grossly and by section, this fibrotic change was characteristic of endocardial sclerosis.

We feel that there are two observations of significance in this heart. The first is that of severe and fatal congenital heart disease, assuming the form of hypoplasia of the left chambers and of the aorta. This deformity, often occurring with aortic stenosis or atresia,

has been described by Abbott and others. It is the situation which Patten[1] describes as "the conspicuously defective development of the left side of the heart which is encountered when, as occasionally happens, abnormal development prematurely closes or markedly narrows the interatrial communication of the fetal heart."

The second observation to be emphasized is the subendocardial fibrosis involving the left auricle and ventricle. This finding is characteristic of endocardial sclerosis. In a recent review, Cosgrove and Kaump[2] have discussed the significance of this disease. They present data on 50 infants, of whom most had lived for a few days, occasional ones having survived for several months, and one child for five years. In all cases, the gross appearance of the heart was distorted to a degree compatible with a diagnosis of congenital heart disease.

Fig. 2.—Photomicrograph of section taken through thickened and fibrotic endocardium of left ventricle. A rather cellular fibrosis without inflammatory reaction, and a single large blood vessel are seen. At the bottom there is normal myocardium.

Microscopically, the lesions ranged from edema and degeneration through varying degrees of fibroelastic thickening and fibrosis of endocardium and myocardium. Thrombus formation, coronary vessel sclerosis, valvular verrucae, round-cell infiltrations, calcifications, and endocarditis were also observed. A controversy exists as to whether endocardial sclerosis represents a form of congenital heart disease caused by an inherent failure in the fertilized ovum or an infection transmitted from the mother. Although these authors have declared in favor of the first interpretation, we are inclined to feel that our case is better explained by infection. It is a heart whose fatal distortion shows no absence or serious displacement of structure, and which seems to be the result of a premature functional closure or stenosis of the foramen ovale. It also shows the characteristic lesion of endocardial sclerosis. We wish to present and emphasize co-incidence of these lesions with proved "infectious" disease in the early phases of this heart's development.

Summary and Conclusions

Recapitulation of the clinical history indicates the following chronologic sequence:

1. Onset of symptoms referable to infectious mononucleosis May 10, with vesperal fever, chills, and arthralgia.
2. Last menstrual period May 14.
3. Diagnosis of infectious mononucleosis established May 20 by positive heterophile test, blood smear, and clinical picture.
4. Presumed date of ovulation and conception based on known history of 28-day menstrual cycle, May 28.

It is clear, then, that this patient had active infectious mononucleosis at the time of conception and during the earliest stages of fetal development. She was observed through pregnancy and was delivered of an infant who promptly died of severe congenital heart disease.

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ASCITES IN PREGNANCY*

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ASCITES associated with pregnancy is an infrequent finding. Modern textbooks make no mention of the condition, whereas textbooks of the nineteenth century give the subject some attention.[1, 2] In a review of the records at Charity Hospital for the last ten years, only one case could be found in 55,000 pregnancies. This patient would probably have had ascites without pregnancy as she had a decompensated syphilitic heart lesion. As far as can be ascertained, pregnancy and ascites are mentioned in the literature thirty-eight times. Of these references, only eleven are in English, in which sixteen cases are reported. The first was recorded in 1791 and the last in 1887.[3-13]

Case Report

Mrs. K. J., Z-5103, aged 25 years, gravida iii, para ii, was admitted to Touro Infirmary at 5:15 P.M. on April 29, 1947.

Past History.—Patient had eclampsia in 1941 and was delivered of a normal male child. The patient's condition at that time was regarded as critical due to a very low urinary output associated with other findings of a severe toxemia. (High fever, rapid pulse and respirations, and high blood pressure.)

Present Illness.—The expected date of confinement for the present pregnancy was June 2. Physical examination and serology were negative. The pregnancy progressed normally until the thirtieth week, at which time a trace of albumin was found in the urine and the blood pressure was 124/90. There was a seven-pound weight gain in five weeks. Slight pretibial edema was noted. At this time she was placed on the following regime: bed rest, salt-free high-protein diet, fluids, ammonium chloride, sedation, and recording of weight and intake and output. The blood pressure was taken daily. Her condition remained satisfactory; her urinary output remained adequate but the albumin increased to three plus. No increase in peripheral edema was noted.

On April 29, with blood pressure of 132/90, a weight gain of three pounds in twenty-four hours was noted. The abdomen was considerably larger and a fluid wave was elicited. The gravid uterus could be balloted. She was advised to enter hospital. Efforts were made to evaluate her condition, having in view the possibility of evacuating the uterus as soon as circumstances would permit.

Laboratory data on Admission.—Red blood count 5,360,000, hemoglobin 15.8 Gm., white blood count 14,800 (polymorphonuclear leucocytes 57 per cent, basophiles 1 per cent, and lymphocytes 42 per cent), serum protein 4.32, nonprotein nitrogen 35 mg./100 c.c.

Three hours and fifteen minutes after admission she was found to be in labor; the abdomen was considerably larger and more tense. Labor progressed normally for a little over two hours when it suddenly ceased. At this time patient complained of nausea, vomiting, and inability to swallow. Examination revealed the cervix 6 cm. dilated and 80 per cent effaced. The membranes were ruptured, removing as much fluid as possible, but no further contractions were initiated. Due to great discomfort, a paracentesis was decided upon. Two thousand seven hundred fifty cubic centimeters of clear colorless fluid were removed, after which the patient was able to swallow, ceased vomiting, and uterine contractions were again

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noted. No cells were found in the ascitic fluid and the nonprotein nitrogen in the ascitic fluid was 22 mg./100 c.c. During this time, 1,000 c.c. of 10 per cent and 1,000 c.c. of 20 per cent glucose were given. Adequate sedation was maintained with 100 mg. Demerol, 1/150 grain of scopolamine and 1½ grains of Seconal.

On April 30th, after eleven hours of interrupted labor, a viable female child weighing four pounds, fifteen ounces was delivered spontaneously. Urinary output since admission to hospital was 760 c.c. and the blood pressure ranged from 140/100 to 160/105.

On May 1, blood pressure was 140/100 to 170/122. Urinary output was 200 c.c. the first eight hours. Two hundred fifty cubic centimeters of two times concentrated plasma were given on two occasions at twelve-hour intervals. During this time, 1,000 c.c. of 5 per cent and 1,000 c.c. of 10 per cent glucose were given. Urinary output for the twenty-four-hour period increased to 4,700 c.c. Laboratory data: urine, 3.5 per cent moist albumin, serum protein, 4.52; bromsulfalein: Control 0 per cent, five minutes 70 per cent, and thirty minutes 25 per cent.

On May 2, blood pressure was 138/76. Urinary output was 5,000 c.c., residual ascitic fluid seemed to be diminishing. Liver was smooth and not tender and could be palpated 4 to 5 cm. below the costal margin. Choline, 1 Gm., and methionine, ½ Gm., ordered three times daily. Laboratory data: urine, 2.5 per cent moist albumin, few hyaline and finely granular casts; serum protein, 4.69; albumin, 2.37; globulin 2.32, cephalin flocculation, one plus.

On May 3, blood pressure was 160/110. Urinary output was 3,400 c.c. Laboratory data: serum protein, 4.63; serum bilirubin, per cent promptness in direct reaction, 100 per cent; cephalin flocculation, negative; bromsulfalein; control 0 per cent, five minutes 30 per cent, and thirty minutes 0 per cent.

Phenolsulfonphthalein test, first hour 60 per cent (300 c.c.), second hour 5 per cent (200 c.c.); Fishberg concentration test, 1.015, 1.017, and 1.017.

On May 6, ascites could not be detected and patient has no complaints. Electrocardiogram was within normal limits and x-ray of chest was reported negative. Patient was discharged for further care at home.

On June 13, blood pressure was 134/100. Urine showed a trace of albumin with an occasional finely granular cast. The liver was smooth, not tender, and could be felt just below the costal margin.

October 22, blood pressure was 130/80. Complained of occasional headache and nocturia (one time). Liver could still be palpated. Urine, specific gravity 1.021, albumin, very faint trace, and microscopic examination negative.

Summary

A case of acute ascites in pregnancy is presented. There is little doubt that this is a true eclamptogenic toxemia of pregnancy. The course prior to this pregnancy and for the first thirty weeks gave no indication of any hypertensive state, albuminuria, or any unusual weight gain. The cause for the ascites can possibly be explained by one or more of the following: (1) low serum protein with alteration in the albumin-globulin ratio; (2) portal block (liver damage demonstrated by comparison of liver function tests taken immediately prior to delivery and five days post partum); (3) hemoconcentration, which is demonstrated by red blood cell counts and hemoglobin measurement taken at the same time as liver function tests, possibly enhanced a portal block by retarding the portal circulation.

The fact that this patient was an eclamptic with her first pregnancy must be kept in mind as the liver may have been sufficiently damaged at that time to reduce the liver reserve to a point where the added load of pregnancy could not be tolerated. This could have been the factor predisposing this patient to another severe toxemia associated with ascites. Liver biopsy was contemplated but not done.

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PRECOCIOUS PUBERTY IN GIRLS

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THE constitutional type of precocious puberty is the most common type.[1] Cases in which the precocity is due to an ovarian tumor are less frequent, and the ovarian neoplasm in such cases is almost always a granulosa cell tumor. In reviewing the literature I find only two cases in which what appeared to be a simple cyst of the ovary was thought to account for the precocity. One was a case reported by Lull,[2] in which the lesion seemed to be a simple follicular cyst; the other case was reported by Mengert,[3] who stated that the ovarian lesion may have been a follicular cyst. In the case now reported below, a simple cyst of the ovary was present.

Case Report

H. W., a Negro girl, was born on Jan. 8, 1931[4] at full term with a normal delivery. She was thought to weigh 7 pounds at birth, was breast fed, walked at 9 months, and talked at 18 months. Dentition occurred at 6 months. She had measles at 2 years, pertussis at 4 years, varicella at 5 years, and mumps at 6 years. There were four siblings.

On May 26, 1937, when she was 6 years, 4 months old, she had vaginal bleeding for the first time. Three months before that she had had a vaginal discharge. Two months before the bleeding, swelling of the breasts had been noted. The first episode of bleeding lasted four days. Bleeding subsequently recurred every twenty-eight days, continuing to last four days each time, and was never very free. However, for three months before admission to the hospital she bled continuously.

Because of the bleeding she was admitted to the hospital on Aug. 29, 1938. At that time she was 7 years, 7 months old. She was well nourished, appeared in good health, and was large for her age. The breasts were precociously developed, and hair was present on the mons pubis. There was a slight bloody discharge from the introitus. This orifice was virginal. Rectal examination revealed an abnormal pelvis mass. An x-ray of the skull was normal. The sella turcica measured 11 mm. in length and 8 mm. in height. Blood counts and urinalysis were normal. The Wassermann reaction was negative. The blood pressure was 100/50. The weight was 76 pounds, temperature 98.6° F., pulse 110, and respirations 22.

A preoperative diagnosis of precocious puberty, probably due to a granulosa cell tumor of the ovary, was made. She was operated upon on Sept. 6, 1938. An ovarian cyst replaced the right ovary. It was thin-walled, filled with thin fluid, and measured 10 cm. in diameter. A right salpingo-oophorectomy was done. The appendix and a small left parovarian cyst were also removed. The tubes, uterus, and left ovary were recorded as being small. The right tube measured 7 by 0.4 cm. The pathologist reported a corpus luteum cyst (Figs. 1 and 2). The patient's convalescence was uneventful.

The follow-up was as follows: May 23, 1940 (aged 9 years): There was no bleeding since the operation. There were no complaints. A keloid of the scar was present. The hymen was intact. A normal infantile uterus was felt on rectal examination. The breasts were larger than normal for her age, and pubic hair was present, but the development of both was less than prior to operation.

Feb. 17, 1944 (aged 13 years): Amenorrhea persisted until the age of 12 when menstruation occurred. She menstruated regularly every month since then, flowing five days. Moderate dysmenorrhea occured. The introitus was virginal. No abnormalities were found on rectal examination.

July 21, 1947 (aged 16½ years): The last menstrual period was April 6, 1947. Weight 116½ pounds, height 60 inches, blood pressure 116/80. The uterus was soft and the size of a ten to twelve weeks' pregnancy.

On Dec. 30, 1947, this patient, lacking nine days of being 17 years old, entered St. Philip Hospital on the obstetrical service and was delivered at term on that day of her first child. She was discharged from the hospital on Jan. 6, 1948.

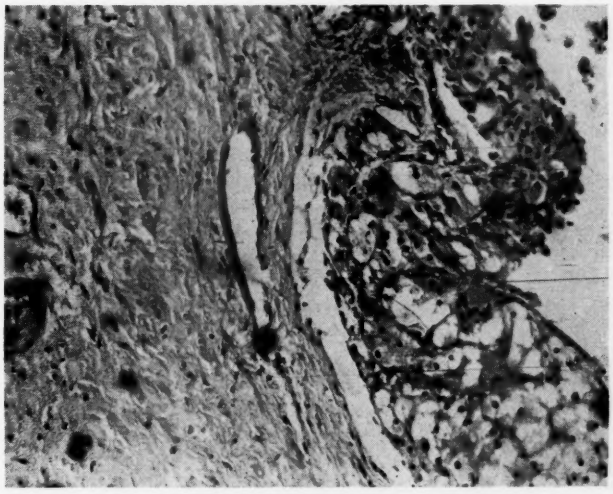

Fig. 1.—Section of ovarian cyst in a case of precocious puberty.

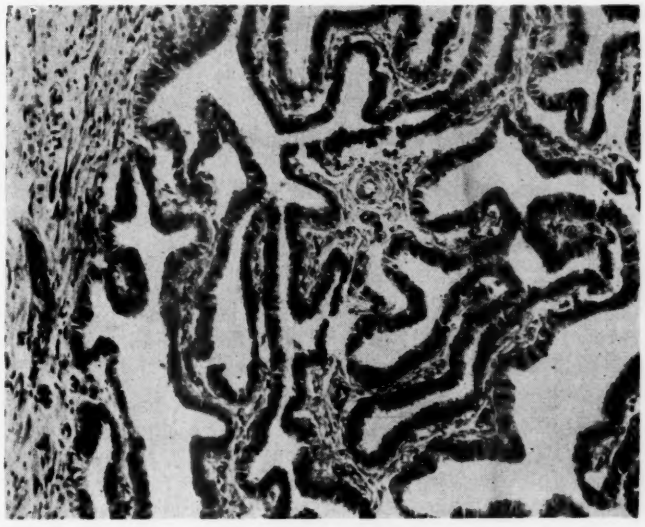

Fig. 2.—Precocious puberty. Section uterine tube, adult type.

Comments

The precocious puberty in this case was obviously not due to a granulosa cell tumor, suspected preoperatively, nor was any true tumor of the ovary found. Nevertheless, considering that a cyst with a diameter of 10 cm. replaced the right ovary and that there was some regression of secondary sex characteristics postoperatively, it was regarded that this patient

had a form of precocious puberty due to the ovarian cyst. However, as this interpretation did not seem entirely satisfactory, Dr. Emil Novak was requested to give his views on the case. He reports[5] his belief that the ovarian condition was a cystic, but normally functioning, corpus luteum, and that the case is one of the constitutional type. He suggests that the subsequent amenorrhea was of the functional type which is seen not infrequently in normal girls in the pubertal or adolescent stage.

Thus is reported a case of sexual precocity associated with an ovarian cyst, but possibly of the constitutional type. It may be that Mengert's and Lull's were similar to this case.

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Hellman, L. M., and Vosburgh, G. R..: Role of Transfusion in the Etiology of Erythroblastosis, J. A. M. A. **136**: 79, 1948.

The authors wish to re-emphasize the fact that Rh compatibility should be determined for all women prior to transfusion and only Rh negative blood should be used in negative cases. They report cases of nine Rh-negative women who gave histories of previous blood transfusions and, as a result of the transfusions, the subsequent childbearing careers of these patients were gravely jeopardized. These nine women had had five normal children prior to their transfusions but had only two normal infants thereafter. Both of these normal children born after transfusion were Rh-negative, these women having heterozygous husbands.

William Berman.

Aldrich, C. Anderson: The Advisability of Breast Feeding, J. A. M. A. **135**: 915, 1947.

Human milk still remains the best type of milk for young infants, although it probably is not always a complete food after the first few weeks. Breast milk has a definite preventive and therapeutic value. It is the safest milk for premature babies who are mature enough to suckle at the breast.

As a technique, breast feeding is probably the best method of providing gratification and a sense of security to the babies. But even in artificial feeding the mother can impart an adequate amount of that security in her manner of handling the infant.

Contraindications include pathologic conditions in the breast or nipple and some disease processes in the mother. Minor objections to breast feeding can best be met during the antepartum care of the patient.

William Berman.

METASTATIC CARCINOMA OF THE URETER IN CARCINOMA OF THE CERVIX

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IN 1933, we reviewed 50 cases of ureteral obstruction occurring in carcinoma of the cervix at the Brooklyn Cancer Institute. We have reviewed the cases which have entered the Institute since that time and the case herein reported is the only one in which either at autopsy or operation metastasis to the ureter was discovered.

Case Report

Case No. 33674, L. R., was admitted to the Brooklyn Cancer Institute on July 7, 1947, with a diagnosis of epidermoid carcinoma of the cervix, Grade III. The patient was a white woman, 40 years of age. She complained of pain in the lower back, radiating to the left leg. Extreme frequency and dysuria were present. When she was admitted, her temperature was 103° F., pulse 110, respirations 28. Extreme weakness and loss of weight were present. The patient had had two previous admissions to the hospital in 1947. All in all, she had received 9,000 mg. hr. of radium, divided into two doses, and administered by uterine tandem with colpostat and cork. Between Nov. 15, 1946, and Feb. 3, 1947, she had been given 6,660 r. units of deep x-ray therapy. On Feb. 21, 1947, urologic examination revealed a normal bladder mucosa. Both ureteral orifices were normal and both ureters could be catheterized without difficulty. Indigo-carmine injected intravenously returned in four minutes from both sides in good concentration. X-ray of the urinary tract and bilateral pyelography were negative. It was noted that there was a bifid renal pelvis on the right side. Following completion of the deep x-ray therapy, the patient was discharged from the hospital on June 1, 1947. She was readmitted on July 7 with the complaints previously noted. The left kidney was enlarged and tender and extreme lumbar spasticity was present. Pelvic examination disclosed the vaginal vault to be definitely contracted. The vaginal mucous membrane was pale; no ulcerations were found. The cervix was not palpable. On rectal examination, a mass the size of an orange could be palpated in the left parametrium. The urine was alkaline in reaction with a specific gravity of 1.024. Microscopic examination revealed innumerable pus and blood cells. Blood count showed a hemoglobin of 14 Gm., 4,700,000 red blood cells and 13,200 white blood cells, with polymorphonuclear leucocytes of 92 per cent and lymphocytes of 8 per cent. The blood urea was 11.5 mg., creatinine 1.2 mg., sugar 130 mg.

On July 9, two days subsequent to the patient's present admission, urologic examination disclosed evidence of a subacute cystitis. The right ureteral orifice was normal. Extreme bullous edema was noted at the left ureteral orifice. The ureteral catheter was obstructed on this side, at a point 2 cm. from the vesical orifice, and the obstruction could not be overcome. The right ureter could be catheterized without difficulty. Indigo-carmine injected intravenously returned in three minutes from the right ureter in good concentration. There was no return of the dye from the left side.

Intravenous urography at this time revealed a large, nonfunctioning kidney on the left side. The right pyelogram was normal.

The temperature remained elevated in spite of the administration of sulfonamide therapy and large doses of penicillin. Pain and tenderness in the left renal area persisted and a diagnosis of ureteral obstruction, with secondary pyonephrosis, was made. A left nephrostomy was decided upon. On Aug. 8, 1947, the kidney was explored under spinal anesthesia. At

operation, a marked perinephritis was noted. The renal pelvis and upper ureter were found to be extremely dilated. An incision was made into the posterior surface of the renal pelvis, followed by a gush of purulent urine. A clamp was passed through the renal pelvis to the renal cortex. An incision was now made over the clamp and a No. 24 F. Pezzer catheter was drawn into the pelvis of the kidney. A cigarette drain was placed in the renal pelvis and the wound closed in layers. Following this procedure the temperature dropped to 99° F. and remained normal. The general condition of the patient definitely improved. At this point it was decided to explore the lower left ureter with the object of transplanting the ureter into the sigmoid. The patient was placed on a low residue diet. Sulfasuxidine was given by mouth. The patient was given daily enemas and two blood transfusions. On September 9,

Fig. 1.

Fig. 2.

Fig. 1.—Retrograde pyelography reveals a fairly normal left kidney. There is no evidence of ureteral obstruction.

Fig. 2.—Intravenous pyelogram taken five months later reveals a nonfunctioning left kidney.

under spinal anesthesia, a left rectus incision was made and the peritoneum opened. Numerous adhesions were encountered; these were separated. There was distinct infiltration of the peritoneum on the left side. The posterior peritoneum was incised at the level of the bifurcation of the iliac vessels, where the ureter was easily isolated. A large periureteral lymph node was palpated and easily removed. The ureter itself was thickened to the diameter of a lead pencil, and could easily be freed to a point about 3 cm. from the bladder. Below this, the ureter was normal in appearance. The ureter was clamped at this point and cut. The distal part was then ligated. The proximal part of the ureter was then brought up for a distance of about two inches and it was found to be completely replaced by solid tumor formation. The tumor-containing portion of the ureter was excised. Above this point the ureter was only moderately dilated, not enough to decide against transplanting it into the

Fig. 3.—Ureteral wall showing destruction of mucosa and lymphatic invasion by nests of tumor cells. (×50)

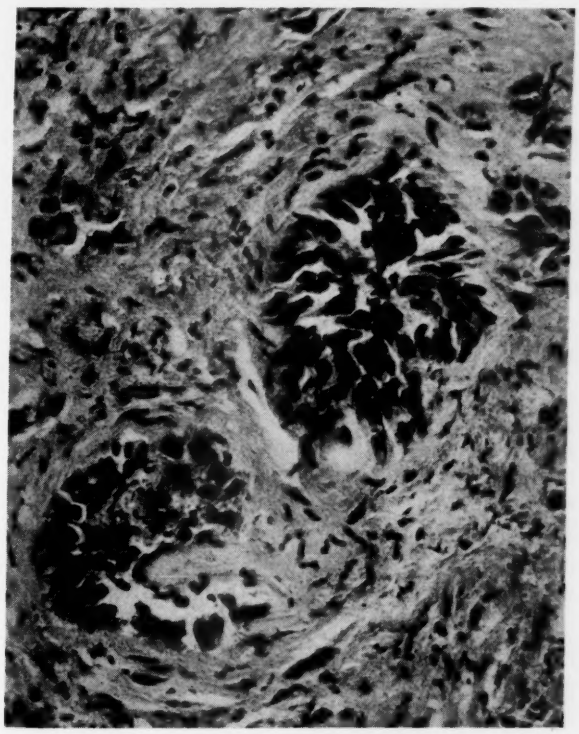

Fig. 4.—Nests of tumor cells in ureteral wall, marked desmoplastic reaction. (×425)

bowel, especially since the nephrostomy tube was to be left functioning. The posterior peritoneum was then closed with No. 00 chromic catgut sutures. The sigmoid could be easily mobilized and the ureter was transplanted into the bowel by the technique of Coffey. The sigmoid was then fixed to the posterior peritoneum by means of two interrupted sutures of No. 00 chromic catgut. A cigarette drain was inserted into the abdomen and the wound was closed in layers.

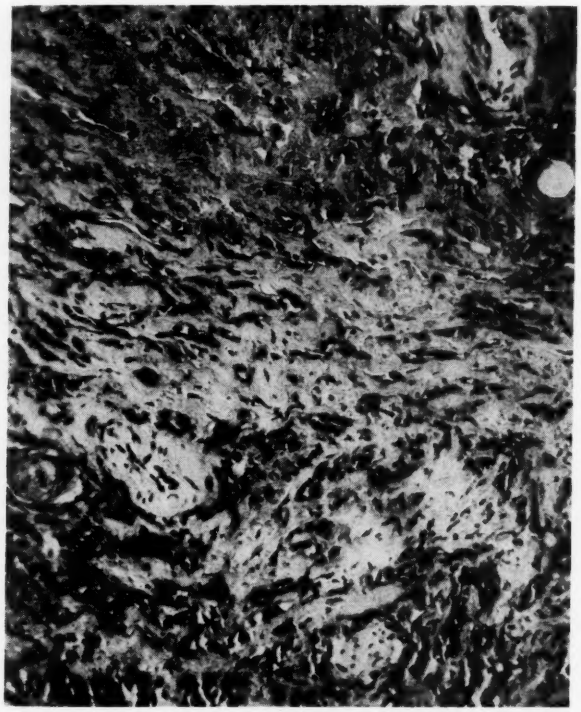

Fig. 5.—Section through periureteral lymph node showing complete replacement by tumor and fibrous tissue. (×210)

Pathologic Report (Dr. Herman Balker).—Left ureter: Section through the ureteral wall shows marked widening and replacement of the muscuar layer by fibrous tissue. There is no recognizable mucosa. All the layers are widely invaded by nests of atypical cells of the squamous-cell type. The nuclei are hyperchromatic and show marked variation in size and shape. Large areas are necrotic.

Diagnosis.—Metastatic squamous-cell carcinoma to the ureter of uterine cervical origin. Section of a periureteral lymph node shows complete replacement of lymphoid structure by sheets of metastatic squamous cells.

There was very little postoperative reaction. On the tenth postoperative day the nephrostomy tube was clamped. Passage of urine through the rectum was noted almost immediately. At this time the nephrostomy tube was removed. The patient was out of bed and up and about the ward, apparently doing well. On Oct. 21, the twenty-fifth postoperative day, the temperature rose to 104° F. The patient complained of pain in the chest and was extremely dyspneic. An x-ray of the chest taken the following day revealed the presence of a bronchial pneumonia associated with partial atelectasis of the left lung. With this the urinary output began to decrease and blood chemistry on October 26 disclosed 100 mg. of urea nitrogen. Intravenous glucose, penicillin, and then streptomycin were given. However, the patient appeared toxic and the temperature continued to run a septic course. She expired on November 15. Autopsy could not be obtained.

Summary and Conclusions

Although it has long been recognized that ureteral obstruction with secondary renal infection and uremia is the common cause of death in carcinoma of the cervix, there is considerable variance of opinion as to the mechanism of this obstructive process. It has been argued by many authors that fibrosis of the lower ureter follows radiation therapy in many instances. There is no doubt that fibrous tissue reaction does take place. However, this process of desmoplasia is a common reaction in carcinomatous invasion and it occurs with or without radiation therapy. The tumor spreads to the periureteral lymphatics and compresses the ureter. Involvment of the ureter itself is rare. Its occurrence suggests metastasis to the lymphatics within the ureter itself.

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Statistics show that in the State of Michigan the maternal death rate has been reduced from 10.47 in 1900 to 1.18 in 1946; and this improvement is nation-wide. This represents a significant scientific achievement. The use of the sulfonamides and, more recently, penicillin has resulted in the most marked decrease in infection as a cause of maternal deaths. But other factors are of importance in reducing maternal deaths, including the increasing use of blood transfusion, hospitalization for delivery, better understanding of the mechanism of labor, and improved prenatal care. There has also been a significant and striking decrease in infant mortality; in Michigan, the infant mortality rate in 1946 was one-fourth of that in 1900. While much of this decrease in mortality (in the first year of life) is credited to the pediatricians, the obstetricians are more directly responsible for the decrease in neonatal mortality. At present, prematurity is the chief factor in deaths in the neonatal period.

The increasing emphasis on prenatal care is one of the important factors in improving obstetric practice; it is a relatively recent development, the present standards for prenatal care having been developed in the last ten years. The great increase in hospital deliveries is also an important factor, as it is only in properly equipped hospitals that the risk from unforseen complications of labor can be reduced. There are some disadvantages of hospital deliveries, such as, in some instances, unwarranted interference with the mechanism of labor, or overseparation of mother and child, with lowered incidence of breast feeding, but such disadvantages can be overcome. There is a tendency toward preventing undue prolongation of labor by the use of episiotomy and outlet forceps. While it may be found that these procedures are not always desirable, they have so far resulted in shortened labors, less exhausted mothers, and fewer maternal birth injuries. Early ambulation of obstetric patients has come back to obstetrics through the results of early ambulation in surgical operations, but the true value of this procedure cannot yet be established, probably not for another decade or two. However great the gains in obstetrics have been, there are many problems to be solved in the future.

Harvey B. Matthews.

VAGINAL CARCINOMA IN A GIRL 14 YEARS OF AGE TREATED BY RADIATION

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SINCE primary carcinoma of the vaginal wall is relatively rare, it is not surprising that hardly half a dozen instances have been reported in patients 20 years of age or under. Moreover, too few of these reports[1, 2] are recent enough and in sufficient detail for use as a guide in treatment. It is true there are to be found in the literature a limited number of individual case records concerning women of more advanced age, and also a few small series of primary vaginal carcinoma.[3-9] In the latter the results almost without exception have been poor, though here, as in other malignancies of the female generative organs, a most important factor appears to have been delay in seeking advice. Even in early or relatively early cases, however, the low survival rates have failed to demonstrate definitely an efficient method of treatment, and surgical removal versus radiation is still considered debatable. Recently the argument seems to have been running in favor of radium plus deep x-ray therapy, particularly if the dosages can be made large, but much is yet to be learned before the situation can be considered satisfactory. Consequently, this case is of interest not only for its rarity, but also because it offers some additional data regarding therapy.

This girl was first seen on May 9, 1942, two weeks before her fourteenth birthday. Approximately regular vaginal bleeding, thought to be menstrual periods, had begun about eighteen months before. A few months before examination, however, bleeding had become almost continuous, though never profuse. Otherwise the history was unessential, as was also the examination except for the pelvic findings. The vagina admitted one finger, with which an irregular, soft mass was palpated in the upper part of the vagina. The possibility of a malignancy involving the cervix was suspected, and exposure by speculum permitted removal of a small piece of tissue. Microscopic sections from this showed advanced, medullary, squamous cell carcinoma.

On May 22, 1942, examination revealed a fungating growth about 3 cm. in diameter arising from the vaginal wall anteriorly and to the right, just below and not involving the cervix uteri. The elevated portion of the growth was curetted away, and 100 milligrams of radium in containers was tightly packed against the lesion. Examination of another piece of tissue confirmed the previous diagnosis. Radiation treatment was continued as described below:

First Series.—May 22, 1942. One hundred milligrams of radium in suitable containers, screened by 1 mm. brass and 1 mm. hard rubber were placed directly against the vaginal carcinoma, the surrounding structures being protected by a lead plate. The dose amounted to 3,600 milligram hours. From May 25 to May 28 supervoltage roentgen therapy was given externally through two portals, one anteriorly and one posteriorly, for the purpose of cross-firing the pelvis. A dose of 300 r in air was given alternatingly over each portal with an intensity of 20 r per minute at a distance of 60 cm. string target distance. Each portal measured 20 by 25 cm. The quality of the roentgen rays was that obtained with 500 kv. constant potential, 7 mm. Cu., 3 mm. Al., and 5 mm. celluloid. The total dose per portal thus amounted to 600 r in air. This was calculated so as to correspond, by including the percentage of transmission from the opposite portal, to a biologic dose of 100 per cent skin unit dose.

Second Series.—This consisted only of supervoltage roentgen therapy and was given from Aug. 14 to 18, 1942. The technique of procedure was identical to that used in the first series.

Third Series.—Only intravaginal radium was applied. On Oct. 15, 1942, 50 mg. of radium, in suitable containers, screened by 1 mm. brass and 1 mm. hard rubber, were placed opposite the site of the carcinoma for a total dosage of 1,800 milligram hours.

With the above treatment the tumor entirely disappeared about three months after the first two series. Two months later, however, it recurred as a small, pedunculated growth at the old site. This rapidly vanished following the second radium application, as described in the third series above.

The patient was last examined on Dec. 30, 1947, at which time there was no evidence of further recurrence. The introitus and vagina easily admitted one finger for about 6 cm., up to the site of the former growth. At that point the vaginal canal was contracted down to a size of about 5 millimeters. With a probe in this opening and the finger in the rectum it could be determined that the vagina above opened up again, and the small but normally situated cervix could be felt. The uterus was about one-third the usual size, and the adnexa were not palpable.

Of interest has been the approximately normal pubic and vulvar hair growth within a year or two after radiation. There has been rather little weight gain (from about 94 pounds to a maximum of 102 pounds), but the body contour has changed so as to resemble that of many women of her age. The breasts, however, are quite small, and there has been no suggestion of menstruation. Vaginal smears stained by the iodine vapor and the carbolfuchsin[10, 11] techniques have shown a persistent and marked estrogenic deficiency reaction of the vaginal mucosal cells.

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INTRA- AND EXTRAUTERINE PREGNANCY

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IT IS the purpose of this paper to report a case of combined intrauterine and interstitial pregnancy in which the intrauterine pregnancy proceeded normally after resection of the cornu of the uterus, and eventuated in the delivery by cesarean section of a normal baby.

T. L., a 28-year-old Negro female, was admitted to the Charleston General Hospital, Jan. 30, 1947, with severe paraumbilical and right lower quadrant abdominal pains. Following the onset of her pains, she had been given a dose of castor oil by her mother and had vomited once. Shortly after the onset of the pain, she felt faint. There had been no definite shoulder pain. Her bowels had not moved since the day prior to admission, and there were no urinary complaints. There was no vaginal bleeding, and she did not think she was pregnant. She had had a normal four-day menstrual period beginning Nov. 18, 1946. On Dec. 18, 1946, she had had a scant two-day period. From Jan. 18 to Jan. 22, 1947, she had had an apparently normal period. She stated that two weeks before admission she had felt "poorly" and her family physician had made a diagnosis of pleurisy. One week before admission she had fallen down a flight of stairs injuring her back. Since then she had remained in bed most of the time. She had six children, the youngest being 6 months old. There had been no miscarriages, operations, nor serious illnesses. The family history was pertinent only in that her mother had had one set of twins.

Physical Examination.—The patient was a well-developed and well-nourished Negro woman with obvious abdominal distress and marked pallor of the mucous membranes. The temperature was 99° F., pulse 86, and the blood pressure 120/80. The abdomen was moderately distended. There was generalized abdominal tenderness with muscle guarding present over the lower abdomen, and marked rebound tenderness. There was no vaginal bleeding. The cervix was pale, firm, smooth, and closed. Because of marked tenderness on examination, the body of the uterus could not be well outlined. One examiner thought that there was a mass adjacent to the uterus in the right side of the lower part of the abdomen.

The hemoglobin was 49 per cent (Hayden), erythrocytes 2,500,000, leucocytes 15,000, with 82 per cent neutrophiles and 18 per cent lymphocytes. Urinalysis showed no abnormalities.

A diagnosis of ruptured ectopic pregnancy was made, but the possibility of secondary hemorrhage from a ruptured spleen was also considered.

Blood transfusions were administered and operation was performed after the patient had received 750 c.c. of blood. The abdomen was entered through a subumbilical left paramedian incision. On opening the peritoneum a very large quantity of clots and fresh blood was encountered. The uterus was enlarged approximately to the size of a ten weeks' pregnancy, and was quite soft. Arising from a broad base at the right cornu of the uterus was an egg-shaped mass measuring approximately 6 by 5 by 4 centimeters. The right tube joined this mass anteriorly at its junction with the uterus. A narrow segment of omentum was attached to the apex of the mass, and beneath this there was active bleeding from a small perforation. The right tube was thickened and congested. There was a corpus luteum cyst in the right ovary.

The free blood and clots were removed. The attached omentum was doubly clamped, divided, and ligated. An assistant was able to control the bleeding by grasping the uterus proximal to the mass. The right tube was doubly clamped, divided, and ligated adjacent to

the mass. Using no. 30 cotton on straight intestinal needles, closely placed mattress sutures were taken anteroposteriorly through the uterus just proximal to the mass. The mass was then coned out of the uterus distal to the mattress sutures. The anterior and posterior muscular flaps thus formed were approximated with interrupted sutures of no. 30 cotton. Reperitonization was accomplished by tacking the right tube over this region with interrupted cotton sutures. The abdomen was closed in layers without drainage. Blood was administered throughout the procedure (a total of 1,500 c.c.), the patient remaining in good condition throughout.

Pathologic report by Dr. W. Putschar was as follows:

There was a mass measuring 5 by 5 by 4 centimeters. On one corner section of the tube was continous with the mass, and that portion measured 2 centimeters. On the other surface there was a portion of omental tissue firmly adherent to the mass. On the opposite corner from the tube a fresh muscular surface was exposed. On section there was an amniotic cavity 2 cm. in diameter filled with clear yellow fluid and containing a fetus 12 mm. long. The cavity was lined by smooth membrane. The wall measured 0.5 to 0.8 centimeter. The cavity apparently was mainly located in the interstitial portion of the tube, as evidenced by the surrounding myometrium. Lumen contained round, partly necrotic chorionic villi. There were laminated clots and fibrin present. The fairly thick mucosal wall was partly disrupted. Diagnosis: ruptured interstitial pregnancy in right tubal corner sealed off by omentum with fetus of about five weeks.

Because of the enlarged, cystic uterus, it was felt at operation that there was combined pregnancy. This impression was confirmed by the absence of vaginal bleeding at any time, as the decidua should have been cast off after removal of the ectopic pregnancy, had there not been a combined pregnancy. A positive Friedman test on the tenth and eleventh postoperative days served as additional confirmation.

The patient's hospital course was uneventful, and she was discharged on the twelfth postoperative day.

She was followed in the outpatient clinic, and no complications developed. Because of the operative weakness of the uterine cornu, it was felt that cesarean section was advisable, so she was readmitted for operation twelve days before her estimated date of confinement.

On Aug. 13, 1947, she was delivered of a living 6 pound, 4 ounce female child by classical cesarean section. Partial left salpingectomy was performed simultaneously for the purpose of sterilization. She was discharged in good condition on her tenth postoperative day.

Discussion

Combined intrauterine and extrauterine pregnancy is uncommon. Frank[4] estimates an incidence of once in every 105 ectopic pregnancies. Since it is estimated that ectopic pregnancy occurs about once in every 300 pregnancies, this would place the frequency of occurrence of combined pregnancies at approximately once in every 30,000 pregnancies. There has been some confusion in review of the total number of cases. Sloat and Peterson,[9] in 1938, arrived at a total of 324 cases. In 1944, Studdiford and Speck,[11] using compilations of Mitra and Ludwig, estimated the total as being between 309 and 368 cases. A condition which is more unusual than combined pregnancy is interstitial pregnancy. TeLinde[12] states that prior to 1893 we have had to rely on autopsy reports, but that subsequent to that time the literature has presented approximately 200 cases. Needless to say, both conditions are sufficiently rare to make the chance of their simultaneous occurrence almost negligible. Even more remote is the possibility of such a combination resulting in the delivery of a viable child.

The literature reviewed by the authors suggests that many cases of combined pregnancy are mismanaged because the condition is not kept in mind. Active uterine bleeding does not exclude an ectopic pregnancy. There is danger in depending on curettage of the uterus and the finding of placental tissues in ruling out ectopic gestation. The mortality rate has been highest in those cases in which the outstanding symptoms have been those of intrauterine pregnancy.[11]

In some of the cases of combined pregnancy, the uterus has been found enlarged at operation and has been removed. In others the uterus has been opened. This procedure could not conceivably do more than satisfy the surgeon's curiosity. Occasionally a dilatation and curettage have been performed prior to a celiotomy for ectopic pregnancy, and an intrauterine pregnancy thus unnecessarily aborted.[3] Such mistakes may be avoided if one bears in mind the possibility of a combined pregnancy. In some cases, the intrauterine pregnancy will abort due to operative trauma, the influence of excessive intraperitoneal hemorrhage, or other causes. In 35 per cent of cases, according to Dolan,[2] and in 40 per cent, according to Morse,[6] the intrauterine pregnancy will proceed to full term.

Comment

We have reported what we believe to be the first recorded case of combined intrauterine and interstitial pregnancy. A brief discussion on diagnosis and management of this and similar conditions has been presented.

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CHORIONEPITHELIOMA ASSOCIATED WITH NORMAL PREGNANCY

GILBERT F. DOUGLAS, M.D., AND O. M. OTTS, JR., M.D., BIRMINGHAM, ALA.
(From Department of Gynecology, Medical College of Alabama, Division of the University of Alabama)

CHORIONEPITHELIOMA is a rare, and usually fatal, disease occurring about once in every 13,000 deliveries.[1] Fifty per cent of chorionepitheliomas are preceded by hydatidiform moles and the remainder by abortions, with a few cases being associated with normal pregnancies. The infrequent appearance and grave prognosis of this condition warrant the reporting of an additional case.

This patient, A. M. D., hospital No. 30,839, an 18-year-old Negro female, gravida ii, para i, delivered a normal child Dec. 9, 1946. Normal menstrual periods were resumed in January, 1947, and recurred at monthly intervals until May 17, 1947. She was admitted to the Jefferson Hospital Sept. 21, 1947, complaining of lower abdominal cramps and bleeding. Examination at that time revealed a pregnancy of approximately two and one-half months, and a diagnosis of threatened abortion was made. She was treated with sedation and bedrest and was discharged. The patient was readmitted Oct. 6, 1947, at which time she was again complaining of abdominal cramps and vaginal bleeding and was treated with sedation and bedrest. Examination at this admission revealed several small ulcerative areas on the anterior vaginal wall. She was next seen in the outpatient department one week later complaining of profuse vaginal bleeding that had begun during the night. Hemoglobin was 33 per cent, with 1,780,000 red blood cells, and she was admitted to the hospital where examination revealed multiple, friable lesions of the anterior vaginal wall that bled profusely when touched.

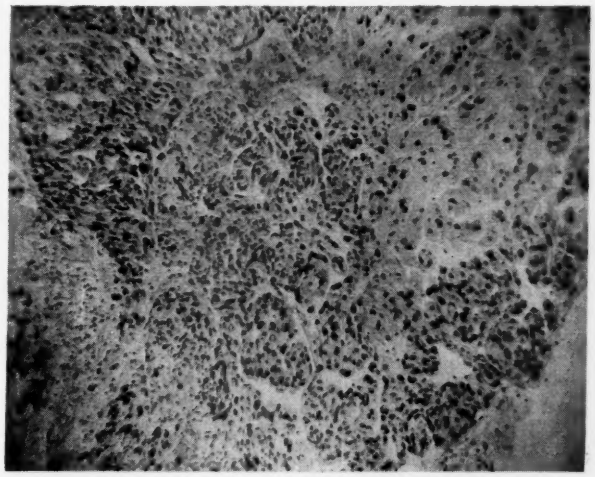

Fig. 1.—Low power study of vaginal biopsy showing malignant trophoblastic cells, mostly syncytial.

Biopsies were taken and reported as chorionepithelioma. The patient at this time was approximately four and one-half to five months pregnant. Fetal heart tones were heard, and a flat plate of the abdomen revealed a small fetal skeleton present. Chest plates showed the presence of metastatic lesions in the lungs. At this time the patient complained of coughing with one episode of hemoptysis.

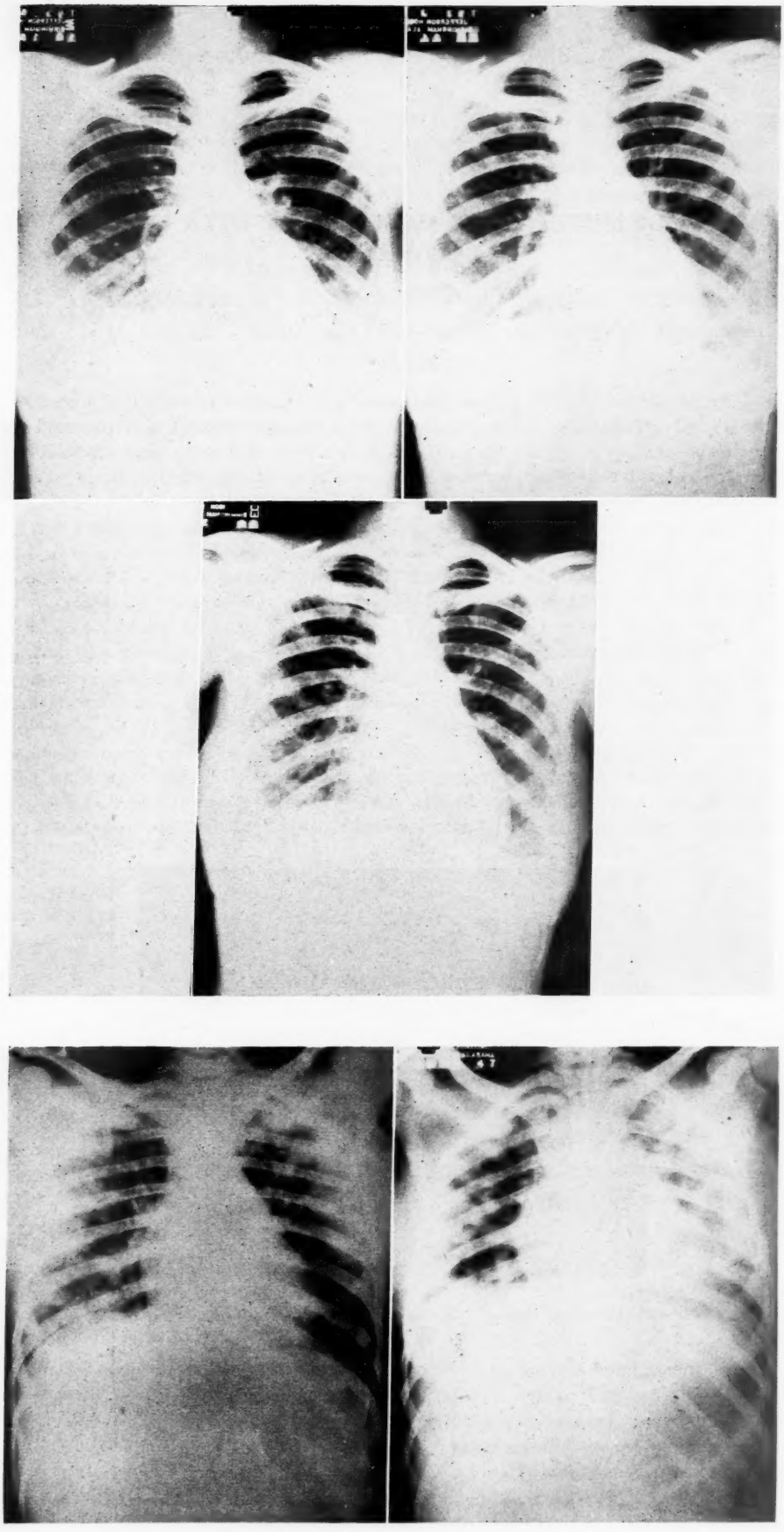

Fig. 2.—Chest plates taken at weekly intervals showing progressive spread of pulmonary metastatic lesions.

It was the opinion of the staff that the treatment of choice in this case would be total hysterectomy, but because of the severe anemia, she was not in condition for such a procedure. It was therefore decided to build up the patient as rapidly as possible with transfusions and

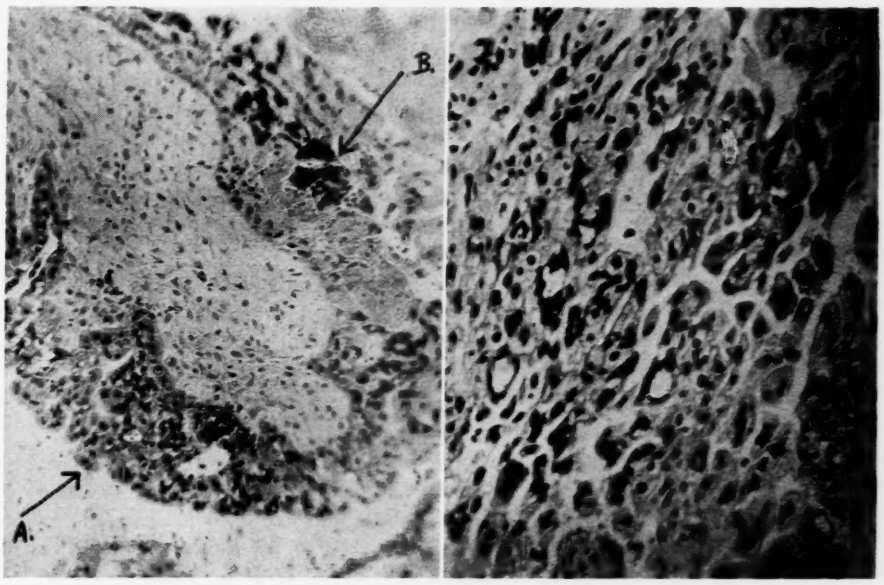

Fig. 3.—Section from the placenta showing trophoblastic hyperplasia and anaplasia. (Low and high power.)

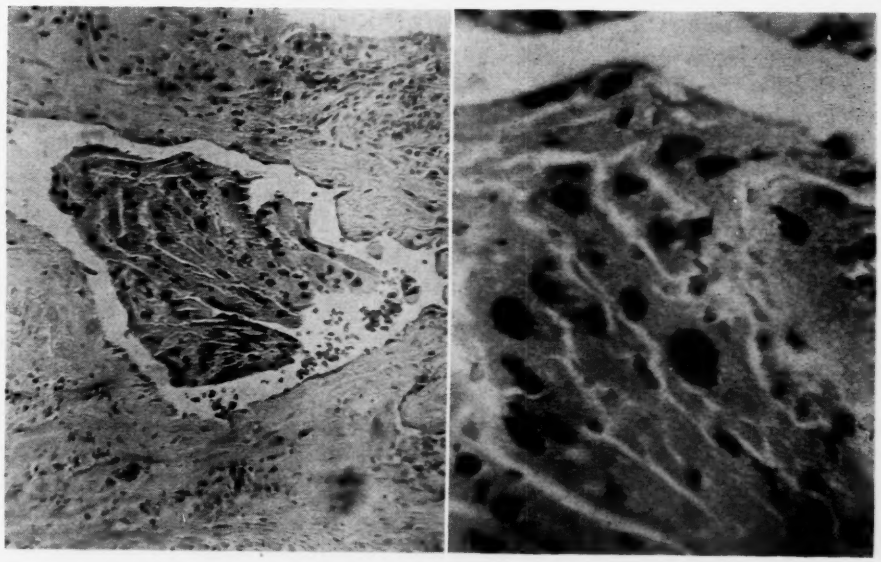

Fig. 4.—Section from the uterus showing malignant cells within a blood vessel. (Low and high power.)

supportive treatment. In the meantime, deep x-ray therapy to the pelvis was begun. She was given 3,500 c.c. of blood during the next twenty-five days before her blood picture attained a level high enough to make surgery possible. Chest plates taken at weekly intervals showed definite metastatic lesions in the chest that were progressive in nature.

A total hysterectomy and a bilateral salpingo-oophorectomy were done on Nov. 6, 1947, with spinal anesthesia. The patient stood the procedure well. The fetus, in spite of deep x-ray therapy, was still viable and was approximately five and one-half to six months old; it expired shortly thereafter. Blood studies on the fourth postoperative day revealed a 32 per cent hemoglobin for which she received 1,500 c.c. of blood. Except for a small abscess of the skin and subcutaneous tissue in the lower end of the incision, her immediate postoperative course was uneventful. X-ray therapy to the pelvis was continued, and radiation to the lungs begun. The patient had two episodes of hemorrhage from the vaginal implants which required packing. Further x-ray studies revealed diffuse metastatic infiltration throughout both lung fields. She had a rapid downhill course and died Dec. 4, 1947, on the twenty-seventh postoperative day. At the time of her death the patient had received a total of 4400 r to her pelvis directed through two anterior and three posterior ports, while 500 r had been delivered to her chest before she expired.

The pathologic report in this case was extremely interesting. The placenta was examined closely by the pathologic department, and a small area of abnormal trophoblastic activity was noted in one villus. The remaining multiple sections through the placenta were entirely negative. Tumor cells were also found within a blood vessel of the uterus at the placental site. Remaining sections through the uterus were entirely negative.

This case brings up the question of where the choriocarcinoma originated. This patient had had a normal pregnancy ten months previous to the present pregnancy. She did not nurse her baby, and normal menstrual periods were resumed. We have no history of miscarriage in the ten months between pregnancies. It is quite unusual to see a choriocarcinoma associated with normal pregnancies. The first evidence of an abnormal condition in what seemed to be a normal pregnancy was the appearance of vaginal metastasis when the patient was approximately three and one-half to four months pregnant. The prognosis in choriocarcinoma is very poor. The treatment of choice is usually total hysterectomy, but even this in early cases offers a poor outlook. This patient on admission was in no condition to stand a major operative procedure. When the patient was finally in shape, a total hysterectomy was carried out in the face of pulmonary metastasis.

Choriocarcinoma is a rapidly metastasizing tumor and very often primary lesions are not found in the uterus.[2] This is well demonstrated in this case because after multiple sections were made through the uterus only one area of malignant cells was noted and these were within a blood vessel. The finding of malignant trophoblastic activity within a small area of the placenta leads us to suspect this as the primary lesion.

This unusual case of chorionepithelioma associated with a normal pregnancy and probably originating in the placenta is presented.

This has impressed upon us very forcibly the necessity for serial sections in determining pathology in obscure cases, otherwise this would not have been found in this case.

We were unable to obtain an autopsy.

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PENICILLIN TREATMENT IN PRENATAL SYPHILIS

CONRAD L. GOSSELS, M.D., MOUNT JACKSON, VA.

THE importance of penicillin treatment in syphilis is well established. Numerous reports prove the advisability of penicillin treatment in different phases of this disease, although no uniformity of opinion has been reached about dosage and best time for treatment. However, there seems to be no doubt about the effectiveness of penicillin in prenatal syphilis as to results for mother and child.

The following case history illustrates the changes in treatment and outlook very clearly:

Mrs. M. N. was 35 years old when she saw me the first time in 1945. She had recently delivered a stillborn baby, four weeks before term. Not satisfied with the diagnosis "kidney trouble" given to her as cause of the stillbirth, she requested a general checkup. Her history did not reveal any venereal infection. On questioning, she remembered that her mother had some positive blood tests years ago, but no details were known. She never was sick. In 1939 she had married. Her husband had never seen a doctor.

Her obstetric history was: her first pregnancy occurred in 1940, and resulted in delivery at term. Baby died at the age of one year. Her second pregnancy in 1941, was terminated by abortion in the third month of pregnancy. Her third pregnancy, in 1943, was terminated in the sixth month. In 1945 she delivered a stillborn baby one month before term. In 1941, when the first baby died, a positive Kahn test was found and treatment started. This treatment was continued over two and one-half years, with an interruption of four months. Three blood tests were taken during this period, but details were not available. The first baby was treated, too, as soon as during a "throat infection" the syphilitic origin was established. The result of blood test when treatment was discontinued is not known. Length of treatment and dosage apparently were not sufficient.

The general checkup in 1945 was completely negative. There were no signs of syphilis present. Kahn test was positive. Antisyphilitic treatment was given, and continued with the cooperation of the patient. In October, 1946, she became pregnant again. At that time the Kahn test was still positive. In February, 1947, twenty-four injections of Mapharsen (14.4 Gm.) and 30 injections of bismuth subsalicylate (4.0 Gm.) had been given. In February, 1947, the fourth month of her pregnancy, penicillin treatment over ten days with 2,800,000 units was given. No further treatment afterwards was considered necessary. In July, 1947, a normal girl was delivered. Mother and baby are in good health at the time of this report, fourteen months afterwards.

TABLE I. SEROLOGIC TESTS

MOTHER										BABY	
1945	1946		1947						1948	1947	1948
12/22	4/24	12/5	4/28	6/12	7/15	8/1	9/2	12/2	6/1	7/16	1/29
plus	plus	plus	doubtf.	plus	plus	doubtf.	neg.	neg.	neg.	neg.	neg.
			0-1-1	4 u	2 u	±2 3					

The serologic tests are shown in Table I. The first sign of a change in the serologic tests was evident in April, 1947, two months after penicillin treatment. But the serologic test did not change to negative before September, 1947, seven months after penicillin treatment and stayed negative thereafter. The good health of the normal baby and the continuance of the negative serologic test in the baby is a gratifying result for the long treatment the mother undertook. Four times pregnancy resulted in death of the baby or fetus, respectively. The fifth pregnancy gave the 37-year-old woman a healthy baby. The effectiveness of penicillin treatment in prenatal syphilis is corroborated by this case.

EPISIOTOMY SCISSORS

FRED HAUFRECT, M.D., HOUSTON, TEXAS

THESE scissors are designed to facilitate the performance of episiotomy, to reduce the amount of blood loss, to judge better the extent of the incision necessary and to protect the fetal head.

Conventional scissors used for episiotomies cut forward, and must be directed downward, or down and laterally, depending upon the type of episiotomy. The handles do not conform to the fetal head as the latter bulges between the labia. In a forceps delivery, there is a more obvious interference by the handles of the forceps.

To offset these difficulties, episiotomies are often done early before crowning, or before the forceps are applied. In such instances, there must be an increase in the amount of maternal blood loss due to the increased interval from the time of the episiotomy to the time of its repair. Also, the presenting part does not bring sufficient pressure to bear upon the perineum to reduce the local blood supply. The opposite of the latter is clearly demonstrated when forceps are applied and the episiotomy is made as traction is applied to the forceps.

An episiotomy done early with ordinary scissors may be either too short or too long. It is more difficult to judge the relationship of the size of the fetal head to the give of the perineum.

This new type of scissors consists of two blades which make an acute angle with the handles. The internal blade (Fig. 1, B) terminates in a blunt tip.

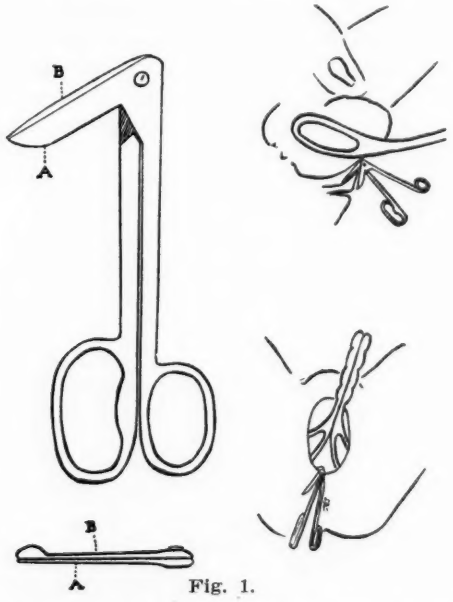

Fig. 1.

When holding these scissors in the conventional manner, the operator cuts in a direction toward himself. The thumb grip controls the external blade (A) which comes in contact with the skin surface of the perineum.

These scissors permit the operator to do the episiotomy at a later period, when the head is crowning in normal deliveries or when forceps are used. This is due to the fact that the handles of the scissors point almost perpendicularly to the skin surface of the perineum, away from the presenting part or handles of the obstetric forceps.

The blunt-tipped internal blade (B) is directed between the fetal head and the perineum with pressure toward the perineum. This avoids injuring the fetal head. There will be no need to insert a finger into the vagina to guide the blade.

I have employed this instrument for almost two years at St. Joseph's Infirmary.

1213 GRAY AVENUE

Correspondence

Uterine Overaction and Its Nomenclature

To the Editor:

I am addressing this letter to you because the various types of overaction of the uterus are difficult to define accurately and different writers use the same name for different clinical entities; this is especially the case when uterine rings are mentioned.

In 1913 I read a paper at the Royal Society of Medicine entitled "The Contraction Ring as a Cause of Dystocia." In it, scattered reports of cases were collected from the literature and I described a specimen which I had obtained by removing the unopened pregnant uterus from a patient in labor. In England, the condition is known as a contraction ring; in the United States, Rudolph and Ivy call it a constriction ring. I think the term contraction ring has the advantage that, in midwifery, contraction is followed by relaxation sooner or later.

At present, the terminology used to describe the various types of uterine rings is in a chaotic state; Rudolph and Fields[1] state that the various current names are: ring of Bandl, contraction of the ring of Bandl, contraction ring dystocia of White, retraction ring dystocia of Pride, simply contraction or retraction ring, uterine contraction ring and constriction ring of Rudolph. Pierce Rucker[2] states that I was the first to differentiate a contraction ring from a retraction ring. This is the reason why I am writing to you on the subject, as I do not seem to have made the differences clear; as an example, I need go no further than the same page of Pierce Rucker's paper where he quotes H. W. Johnson's contribution on "Delay in Labor Caused by Mild Degrees of Bandl's Ring." In my opinion, this is an impossibility as the retraction ring of Bandl could never cause delay in labor.

In obstructed labor, the fetus acts as a splint which keeps the length of the uterus constant and, since each contraction in the second stage of labor is followed by slight retraction, it follows that in the course of hours the upper segment becomes retracted and thicker; since the fetus is keeping the length of the uterine cavity constant, the lower segment must become thinner. There is no other way for the upper segment to become thicker while the length of the uterus remains constant except by thinning of the lower segment. The importance of the fetus acting as a stretcher and maintaining the length of the cavity of the uterus is stressed, as it is an important part of the process of obstructed labor. It is interesting to speculate what would occur if the fetus were absent, as in the utterly improbable case of the uterus trying to expell a large hydatidiform mole through an occluded cervix.

Seeing that the essential condition of the uterus of obstructed labor is one of retraction, it is usual to call it "tonic retraction of the uterus," although, unfortunately, it is sometimes referred to as "tonic contraction." This is a misnomer as, in midwifery, contraction suggests a subsequent relaxation which never occurs in the uterus of obstructed labor, so it is better to speak of either the uterus of obstructed labor or tonic retraction.

Tonic retraction is a slow process taking six or more hours in the second stage to develop. Except in the rare cases of pathological obstruction of the cervix (e.g., a cervical fibroid), tonic retraction does not occur in the first stage of labor or when the membranes are intact; it is a late second-stage phenomenon and is caused by disproportion. The mother's general condition is bad, with raised pulse and temperature, the abdomen is very tender and, per vaginam, the presenting part has a big caput and is fixed. As the placental site is continuously retracted, the fetus dies from lack of oxygen and so the fetal heart is never heard during tonic retraction.

The junction of the retracted, thickened upper segment with the thinned, tense, distended lower segment is the retraction ring or ring of Bandl. The thickened upper segment takes 2 cm. or more gradually to merge into the thinned lower segment, but there is

not any projection on the peritoneal aspect and nothing that could be palpated. During a laparotomy late in obstructed labor, the junction of the two segments is not a noticeable thing and it certainly does not project on the surface of the uterus. Such operations are rare in this country, but Dr. Mahmoud Ismail Bey, Professor of Obstetrics in the University of Cairo, in a personal letter, says, "As regards my opinion about the 'projecting' ring of Bandl at the junction of the upper and the lower segment, I can say that I have done cesarean sections often for women long in labor in whom the lower segment was overstretched but I did not notice or feel such a projecting ring. In many cases the top of the bladder was high enough to be felt as a ridge." There are several excellent specimens

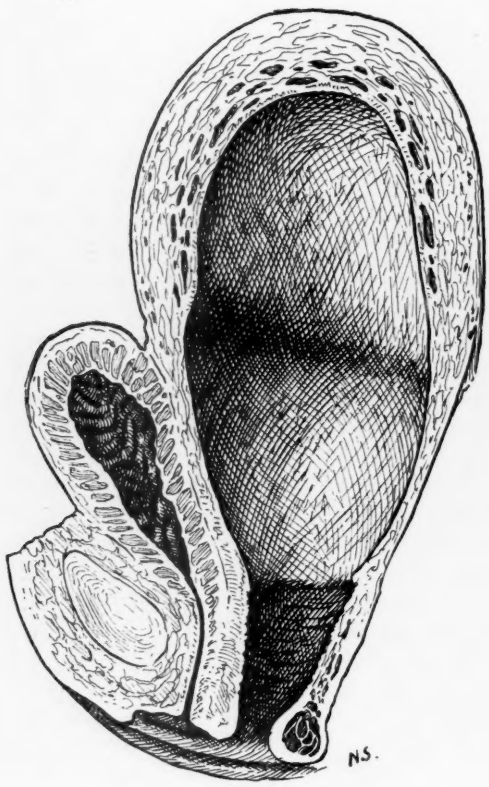

Fig. 1.

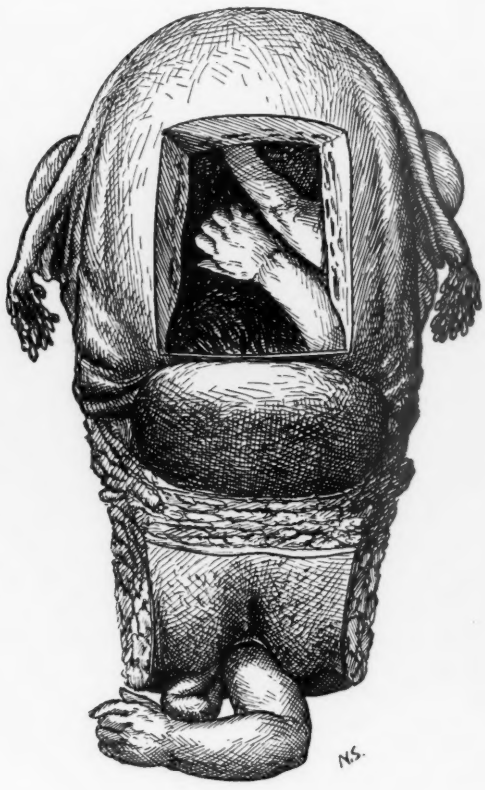

Fig. 2.

Figs. 1 and 2.—Two sketches from a postmortem specimen to show that the ring of Bandl does not form a palpable ridge but the raised edematous bladder does form an easily palpable mass which rises during labor.

of the uterus in tonic retraction in the famous Mahfous collection in the museum of the Kasr el Aini Medical School in Cairo, which confirm my views that it is improbable that anyone has ever palpated the junction of the upper with the lower segment or felt it as a projecting ridge. Yet, for years it was taught that the retraction ring could be palpated through the abdominal wall and could be noticed to rise higher and higher in the lower abdomen while the patient was watched. In my opinion the ridge which they palpated was the top of the edematous bladder which is attached to the lower segment and would certainly be found to get higher as the obstructed labor progressed. Figs. 1 and 2 from a postmortem specimen in the Mahfous collection show that this is the truth.

The upper segment having become retracted and thick and the lower segment thinned, nothing will get them back to their normal state except the delivery of the baby and the involution of the uterus. No drug could possibly alter this condition back to the normal and, thus, as a corollary, if the use of a drug such as morphine appears to alter a

tonically retracted uterus into a normally acting one, it immediately proves that the uterus was not tonically retracted but that some other condition, such as an irritated uterus, was present. Morphine is most valuable in slowing uterine action and thus preventing the rapid progress of retraction but it cannot alter the condition already established. If this is recognized, it will prevent people from stating that tonic retraction has been cured by any treatment other than the removal of the fetus that was splinting the uterine cavity.

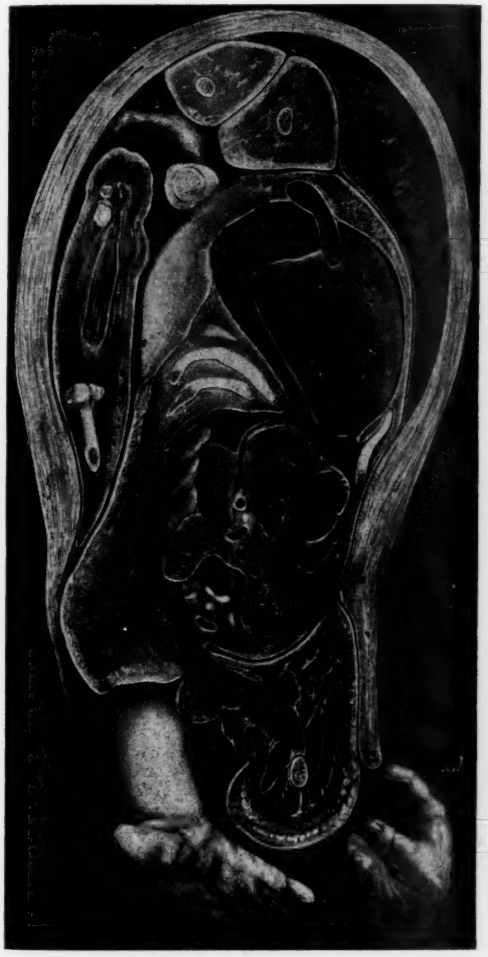

Fig. 3.

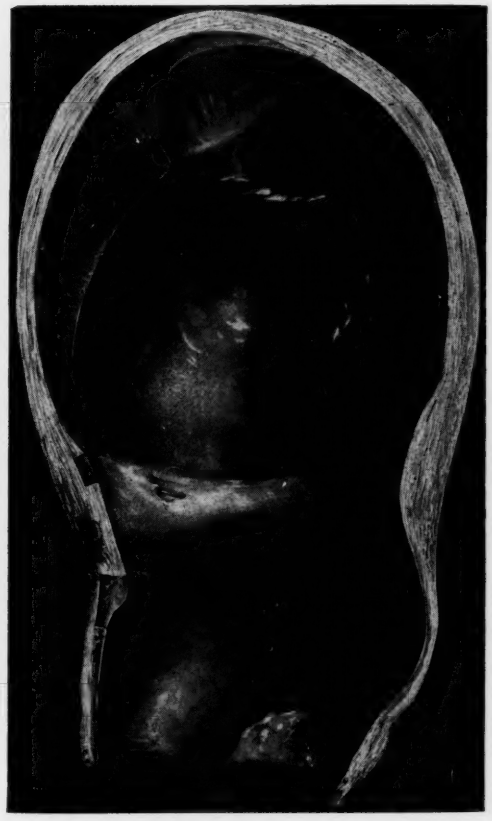

Fig. 4.

Fig. 3.—Mesial sagittal section of uterus with fetus in situ. The child was presenting by the shoulder, and a foot had been brought down in an unsuccessful attempt to perform version. The contraction ring can be seen running obliquely across the uterus. The upper uterine segment is not thickened and the presenting part was not fixed in the brim of the pelvis.

Fig. 4.—Mesial sagittal section of uterus removed during labor, showing contraction ring which caused dystocia.

The end of untreated obstructed labor is death, either from exhaustion or from rupture of the uterus; it is perhaps justifiable to regard tonic retraction as Nature's method of killing fairly quickly a patient with an insuperable obstacle to delivery. Fortunately, secondary uterine inertia does not occur in the second stage of a labor complicated by bony obstruction; if it did, the patient's agony would be prolonged for many days. Yet any examiner knows how frequently students state that there are two alternatives in a case of obstructed labor, either tonic retraction or secondary uterine inertia. Luckily, the statement is not true.

Textbooks tell us that one of the causes of tonic retraction is the use of stimulants to uterine action, such as ergot or Pitocin, but this is improbable. Tonic retraction is essentially a slow process and insidious in its onset, whereas the action of Pitocin is prompt. It is possible that oxytocic drugs may increase the force of uterine contractions and so, in the presence of an obstacle to delivery, make the onset of obstructed labor quicker than it otherwise would have been, but that is all. In the absence of disproportion, all that oxytocics could do would be to produce an irritated uterus, i.e., a generally contracted uterus where the whole uterus is contracted but there is not any thinning of the lower segment. Another way in which a generally contracted (irritated) uterus can be produced is by manipulations, for example, when attempts are made to dilate the cervix manually or when the forceps is applied to the head above the brim and unsuccessful efforts made to deliver the child. In such patients, it is sometimes found that the uterus does not relax and such a case can easily be mistaken for one of tonic retraction, but, after an interval, the uterus is found to be contracting and relaxing normally. A little consideration will show that tonic retraction could not have been present in such patients because it comes on gradually and is never followed by relaxation or by normal uterine action; also, the lower segment is not thinned or tense and the general condition of a patient with a generally contracted uterus remains good. Morphine will assist an irritated uterus to become normal again more quickly than it otherwise would. Although the long-continued contraction of the irritated uterus makes it feel hard, the contraction does not seem sufficient always entirely to stop the circulation through the placental site and so a living child may be obtained after an interval. In tonic retraction the circulation through the placental site has failed and so the child is dead.

A contraction ring is a localized contraction of the uterus which frequently forms over a depression in the child's outline but may be below the child. It occurs in the first, second, and third stages of labor and even before there are signs that labor has started. Hence, it is not the result of labor obstructed by disproportion, and, if disproportion happens to be present, its presence is a coincidence and not a causal factor. The body of the uterus above the ring continues to contract and relax as in a normal labor. The patient's general condition is quite good—several of my patients had a pulse rate of 80. The circulation through the placental site is maintained and so the child is alive.

The cause of the condition is obscure; the causes mentioned in my original article are not truly etiological factors. A contraction ring does cause delay in labor.

Occasionally a contraction ring can be palpated through the abdominal wall as a depression running across the lower part of the uterus. It is usually tender and sometimes the patient states that she notices the discomfort of a uterine contraction first in the region of the ring. If the head is presenting, it is lifted up during a pain and so becomes more mobile from side to side as first described by Gilliatt. On vaginal examination, signs of disproportion are absent. In the majority of cases, the failure of traction by the forceps is the first thing to show that an abnormality is present. Moreover, when the forceps has drawn the head down, it recedes to its original level in the pelvis as soon as traction is stopped. The reason for this recession of the head is that the forceps pulls down the whole uterus containing the child and the resilience of the cardinal ligaments takes the uterus and its contents back to their original level as soon as traction is stopped. In a similar way, the head does not descend during a pain. These signs are an indication for passing the hand into the uterus when the ring will probably be felt round the child's neck.

The treatment of contraction rings has been fully discussed by Rudolph in various papers and so will not be further touched on here.

CLIFFORD WHITE.

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LONDON W 1.

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The Significance of the Nuclear Structure in the Vaginal Secretion Cells as a Means for Cancer Diagnosis

To the Editor:

The papers by Papanicolaou, G. N. (Am. J. Obst. & Gynec. **51**: 316, 1946) and by Ayre, J. E. (Am. J. Obst. & Gynec. **53**: 609, 1947), which emphasized the importance of the nuclear characters for recognizing the neoplastic elements, stimulated me to extend my investigations, which had reached the study of the nucleus of the malignant cell (Tumori **33**: 10, 107, 178, 1947, and Quaderni di Clin. Ost. e Ginec. **2**: 9, 1947), to an interpretative complement of the observations carried out in them.

Meanwhile, Papanicolaou took into consideration the cell as a whole, with techniques not exclusively designed for nuclear examinations. I was stimulated by the observation that the complex of the characters denoting malignancy is indicated by abnormalities, specifically connected with the metabolism of nucleic acids. From the views expressed by Caspersson, T., and Santesson, L. (Acta Radiol. Suppl. **46**: 1, 1942), and by Koller, P. C. (Nature **151**: 244, 1943, Brit. J. of Cancer **1**: 38, 1947, and Symp. Soc. Exper. Biol. **1**: 270, 1947), I reached the conclusion that the neoplastic cells are recognizable from the structure of the resting nucleus. This is distinguishable in two main phases, i.e., when they are overcharged with thymonucleic acid (termed A, with small and not always recognizable nucleoli), and undercharged with thymonucleic acid (B, with well-developed nucleoli). It is clear that the former correspond to the prophaselike cells noted by Papanicolaou. Generally speaking, my conclusions do not differ from those expressed by the American author. Only I go further, interpreting the A nuclei as the resting stages of proliferating cells, and the B ones as belonging to cells in a prenecrotic stage. Finally, I proved that both cellular types are generally mixed together in a tumor, so that I do not, therefore, agree that the B cells are typical for distinct tumors. The observation of mitoses does not often offer any particular interest for diagnosis, owing to the rarity of the mitosis itself and its frequent normality.

The technique used by myself is based upon the compression, as adopted by the chromosome investigators and not on the simple smear. By this means, the cells (previously fixed with two-thirds 96 per cent alcohol, one-third acetic acid for many hours, where the secretion may remain indefinitely, practically without damage) are transferred into a drop of saturated acetic solution (50 per cent acetic acid in distilled water) and carmine powder. The material must remain there for one to two hours. Later, by means of a pipette, it is transferred to a slide, previously covered with a thin film of egg albumin and dried. A cover slip is put on and pressed down without smearing. Finally, by means of a needle, the material is crushed and the superfluous liquid absorbed with blotting paper. This preparation must be observed by green light. A technique is also employed for making the slides permanent, which is too long to refer to here. The microscopic field offers for observation naked nuclei, in the best conditions for revealing the finest structures. The Feulgen reaction can be substituted for the acetocarmine.

The technique used by other authors does not permit observation of the nucleus under favorable conditions, because it gives only a general appreciation of the cell as a whole. For that reason my technique may be more advisable, owing to the fact that the diagnostic characters are seen chiefly in the nucleus.

The technique which I have described must be considered, therefore, as a specialization of that proposed by Papanicolaou, who was the first to give consideration to the value of the cellular structure for diagnostic purposes.

This method has been used with success for making diagnosis of uterine tumors. Up to the present time, the results of the nuclear diagnosis are in agreement with the histologic and chemical features.

Dr. Luigi Cusmano.

Clinica Ostetrica e Ginecologica
della Universita di Parma
Italia

May 18, 1948.

Department of Reviews and Abstracts

Selected Abstracts

Cancer, Malignancies

Cusmano, L.: Distribution of "A" Proliferative and "B" Regressive Nuclei in Cancer Tissue, Tumori 37: 108, 1947.

Cusmano reports in this paper relative frequency of proliferative "A" and regressive "B" nuclei in five cases of cancer of the cervical canal, four cases of cancer of the intravaginal portio of the uterus, and in three cases of carcinoma of the fundus.

The material was prepared by his crushing carminacetic method and by Feulgen microchemic reaction for demonstration of timonucleinic acid. Ten different portions of each tumor were examined and cellular areas were selected for analysis. Frequency of mitotic figures appeared to be closely correlated with the amount of proliferative nuclei. Mitoses were practically absent from areas showing prevalence of regressive nuclei.

Regressive nuclei were prevalent in the three cases of cancer of the fundus. Proliferative nuclei, instead, predominated in the five cases of cancer of the cervix, while in the cancer of the portio (which Italian pathologists classify separately from the cancer of the cervix) proliferative nuclei were more numerous in one case, regressive nuclei prevalent in the remaining cases.

No definite correlation was evident between degree of maturity estimated from the histologic pattern and distribution of proliferative versus regressive cells.

GEMMA BARZILAI.

Cusmano, L.: Mitotic Figures in Cancer of the Fundus and Cervix, Tumori 37: 185, 1947.

Cusmano reports findings of mitotic figures observed in nine cases of cancer of the cervix and in three cases of cancer of the fundus, prepared with the crushing acetic-carmine method and Feulgen's microchemic reaction.

Normal and abnormal mitoses have been found present in the material. Prophase, prometaphase, the long-lasting early phases of mitosis are frequent, anaphase, and telephase, the short-lasting phases of division of the nucleus into daughter nuclei (when details of the process are most evident) are rare.

Neither prophase nor metaphase showed appreciable deviation from corresponding phases of division in healthy cells; typical early aspects of prophase similar to the proliferative "A" cell nuclei, but with some incipient dissolution of the nuclear membrane and more condensed appearance of the chromomeres were seen, as well as late prophase showing dissolution of nuclear membrane and split chromosomes, and metaphase with evenly distributed chromosomes at the equator of the nucleus.

Anaphase and telophase, however, were present showing atypical aspects: anaphase and telephase with aploid, tetraploid and polyploid number of chromomeres, and also showing definitely deviated features such as deletion of parts of the individual chromosomes, inversions, and translocation of single or multiple individual chromosomes, were seen. Altogether, 196 mitoses were observed; 32 appeared normal, 54 showed irregularities in the number of the chromosomes, but only 10 showed definite deviations from healthy nuclei, such as deletion, inversion, and translocation of chromosomes.

This significant paper throws light on the interpretation of mitotic figures in cancer cells; it shows the similarity of proliferative "A" nuclei to early prophase and gives evidence of the rarity of mitosis showing features that can really be considered pathognomonic for a neoplastic growth.

GEMMA BARZILAI.

Cusmano, L.: Nuclear Structures in Normal Villi, Hydatidiform Mole and Chorionepitheliomas, La Ginecologia Scritti in Onore del Professor E. Cova.

In this paper, Cusmano reports observations made on the chorionic epithelium of normal placental villi, simple hydatidiform moles, and chorionepitheliomas stained with his own carminacetic dye and treated with Feulgen microchemic method which reacts positively only with the timonucleinic acid present in the chromomeres.

In normal villi, chorionic epithelium appeared to have uniform elliptical nuclei, with regular nuclear membrane, intensely ccolored and Feulgen-positive, regularly disposed granules corresponding to chromomeres, and a single large, round, Feulgen-negative nucleolus.

In the hydatidiform mole, nuclei show striking variation in shape; some are round, some are elliptic; most of them have a coarse chromoneme with intensely stained granules, giving a strongly positive Feulgen reaction, and one or two faintly stained and Feulgen-negative nucleoli. These nuclei definitely recall the "A" nuclei of proliferative cells of neoplastic tissue. They show, however, a more marked content of timonucleinic acid.

Among these proliferative nuclei, some identical with the regressive "B" cells of neoplastic tissue are seen and faintly show chromomeres and large clumpy Feulgen-negative and intensely red-stained nucleoli.

In the chorionepitheliomas, proliferative "A" nuclei and regressive "B" nuclei are evident and are identical to those seen in cancer tissue. GEMMA BARZILAI.

Massey, E., Dockerty, M. D., and Masson, J. C.: Malignant Lesions of the Uterus Associated With Estrogen-producing Ovarian Tumors, Proc. Staff Meet. Mayo Clin. 23: 63, 1948.

Two cases are reported in which adenocarcinoma of the uterine fundus was associated with an estrogen-producing tumor of the ovary—granulosa-cell tumor in one case and theca-cell tumor in the other, both of which showed areas of malignant degeneration. These two cases bring the number of malignant lesions of the uterus associated with estrogen-producing tumors of the ovary observed at the Mayo Clinic to 15 cases. In 87 estrogen-producing tumors of the ovary observed at the Clinic, the incidence of malignant tumors of the uterus was 17.2 per cent, or, excluding two cases of cervical carcinoma, 14.9 per cent. These figures are in close agreement with similar series reported by others. Several clinical and pathologic observations indicate that malignant lesions of the endometrium do not develop without accompanying hyperestrinism. Only one case has been reported (by Fremont-Smith and his associates) in which proved malignancy of the endometrium followed prolonged estrogen therapy for menopausal symptoms. It is probable, however, that many women have received equally prolonged estrogen therapy without developing carcinoma of the uterine fundus. The occurrence of episodes of uterine bleeding in such cases often leads to discontinuance of the estrogen therapy or reduction in dosage.

In the discussion of this report, Dockerty stated that, in the series of granulosa-cell and theca-cell tumors of the ovary observed at the Clinic in which the incidence of uterine carcinoma was 17.2 per cent, the incidence in 55 postmenopausal patients was 27.3 per cent, an incidence more than 100 times as high as would occur if the two lesions were merely coincidental. Granulosa- and theca-cell tumors of the ovary rarely recur after local removal or metastasize if well encapsulated at the time of operation; and uterine carcinoma is rarely associated with these tumors in patients under fifty years of age. Therefore, local removal of these tumors when encapsulated is indicated in younger women; but if the tumor is poorly encapsulated or ruptured or the patient has reached the menopause, panhysterectomy is indicated with postoperative roentgen-ray treatment only in the case in which there is a possibility or probability of peritoneal soiling with malignant cells. HARVEY B. MATTHEWS.

Irons, W. E., Judd, E. S., Jr., and Dockerty, M. B.: Endometrioma of the Cecum, Proc. Staff Meet. Mayo Clin. **22:** 530, 1947.

Endometriosis of the cecum is rather rare. In a review of 2,062 cases of endometriosis at the Mayo Clinic seen from 1923 to 1943, Masson and Cauker reported 14 cases in which

the cecum was involved. In a study of the pathologic specimens at the Clinic, two specimens of endometriosis of the cecum were found, which clinically could not be distinguished from carcinoma.

In the case reported, the patient was a woman 29 years of age. Her menstrual periods had been regular, the flow lasting four to five days. For six years before admission to the Clinic, she had had premenstrual pain that had subsided when the flow started. At the time of the last menstrual period before admission, pain had been more severe and was accompanied by abdominal tenderness that localized in the right lower quadrant. Six days before admission, pain recurred, at first generalized over the lower abdomen, then localizing in the right lower quadrant, accompanied by nausea and vomiting; two days later, the regular menstrual period began. On admission to the Clinic, nausea, vomiting, diarrhea, pain, and tenderness in the right lower quadrant were present. The patient was kept under observation for seven days, but, as nausea and anorexia persisted and there was slight pain and tenderness over the McBurney area, operation was done. The uterus was of normal size and position, but showed a subserous fibroid on the posterior wall; the left ovary was enlarged owing to a simple cyst from which clear fluid was expelled on puncture; no endometrial implants were found. The cecum was bound in the pelvis by adhesions that appeared to be recently formed. There was a slight inflammatory reaction around the appendix and appendectomy was done. The base of the appendix was inverted. A hard nodule was palpated in the wall of the cecum and was considered to be possibly malignant. Immediate biopsy of a small section showed an endometrioma; and a local wedge excision including normal tissue well around the tumor was done. No further signs of endometriosis were found. The patient made a good recovery; and subsequent menstrual periods have been normal and painless. HARVEY B. MATTHEWS.

Murphy, G. H., and DuShane, J. W.: Mesodermal Mixed Tumor of the Vagina, Proc. Staff Meet. Mayo Clin. **23**: 22, 1948.

In the case reported, the patient was a child of 33 months of age. A year previous to her admission to the Clinic, blood had been noted around the vulva and examination showed a tumor of the vagina. This tumor was removed and reported to be histologically a botryoid sarcoma (rhabdomyoma). Radium and roentgen-ray therapy was employed postoperatively, but there was a recurrence of vaginal bleeding after several months, for which more radiation therapy was employed. When admitted to the Clinic, the child showed no signs of distress. Examination showed a mass in the vagina, and at operation a soft polypoid tumor ws found to fill the vagina. Frozen sections showed a high-grade malignancy, but, as the tumor had infiltrated the vaginal wall, only local removal was done. The tumor had the appearance of a group of fused polyps—the typical "botryoid" tumor. Histologically, it consisted of myomatous-appearing network, with some cellular areas; some of these areas showed spindle cells with mitotic figures, others showed young striated muscle cells with some embryonic myoblasts; there was no cartilage or bone, but some areas of the tumor contained collagen. This is the first case of a tumor of this type observed at the Mayo Clinic.

Mesodermal mixed tumors occur in the uterine body, the cervix, and the vagina. The reports in the literature on the nature and incidence of these tumors are confusing. The relative incidence of the tumors in the various sites is difficult to determine, but the vaginal tumors appear to be the most common. The vaginal tumors have been found only in young children, mostly in those under three years of age. The prognosis in mesodermal mixed tumors, whether of the uterus, cervix, or vagina, is bad; the mortality has been given as 95 per cent; the prognosis in the case reported is considered to be "extremely grave."

HARVEY B. MATTHEWS.

Grattarola, R.: Chromosomes and Nuceoli in Humann Cancer Cells During X-ray Treatment, Tumori **21**: 321, 1947.

In the Department for Cellular Pathology of the Medical School of Milano, Grattarola studied the nuclear changes occurring in human cancer during x-ray treatment with Feulgen, Unna, and Barigozzi-Cusmano staining procedures.

The material was obtained from 21 cases of cancer of the cervix, four cases of cancer of the vagina, five breast cancers, one cancer of the vulva, and two skin cancers.

The above procedures are selective staining methods based on the fact that chromosomes are largely made up of euchromatin which chemically is timonucleinic acid mixed with a globulin-like substance and is different in its staining properties from the heterochromatin which is present in the nucleoli (plasmosomes) and in the cytoplasm, and is chemically made up of a less complex nucleoprotein called ribonucleinic acid mixed with some timonucleinic acid and a large amount of histones. Eucromatin and heterochromatin also differ in their morphologic structure: when fixed and stained, euchromatin appears disposed in tiny regular discs connected by a delicate strand of a material called linin, which has practically no affinity for dyes. Heterochromatin is made up of irregular clumps.

The content of euchromatin and heterochromatin varies in the nucleus according to different phases of its development and life; it also varies according to the nature of the cell. Nucleoli, which are made up of heterochromatin, appear most evident during telephase of mitosis when chromosomes become indistinct and disappear in the prophase when chromosomes became condensed. This has been interpreted as an indication of exchange of material between euchromatin and heterochromatin. Heterochromatin provides the chromomeres with the material they need for reproduction, but this material which is chemically ribonuclein, must be transformed into timonuclein in order to be active. If the capacity to effect this transformation is lost, the cell loses its capacity to reproduce. If in a cell nucleus heterochromatin is prevalent, this means that the normal balance of transformation of ribonucleinic acid into timonucleinic acid is impaired, diminished, or lost. X-ray treatment aims at the destruction of reproductive capacity of cancer cells: content and disposition of ribonucleinic acid in the cell are, therefore, a fair indication of the action of x-ray on cancer. By staining cells with selective stains for ribonucleinic acid and timonucleinic acid, the action of x-rays on the cell nucleus can be followed during treatment.

With all three staining methods, Grattarola could demonstrate that in cancer cells at rest timonucleinic acid is predominant and that during irradiation the euchromatin was substituted progressively by the heterochromatin: chromomeres became less and less evident, active nuclei capable of reproduction were transformed into inactive, regressive formations, and this regression could be actually followed, step by step. The importance of this observation can hardly be overestimated.

Barigozzi's method appears to be the simplest and quickest, so that it may become an exceedingly satisfactory means of investigation for the diagnosis of cancer as well as for estimation of the action of x-rays in malignancies.

Stained with Feulgen, timonuclein appears a more or less dark violet, depending on the amount present; ribonuclein is not stained at all; with Unna's method, ribonuclein appears red, timonuclein violet; with Barigozzi's and Cusmano's method morphologic as well as staining differences are apparent. Cells with high content of timonucleinic acid, called "A" cells, show a well-defined nuclear membrane and chromomeres appear as distinct, intensely red granules, while nucleoli appear as light pink vesicular bodies. Cells with high ribonucleinic acid content show an irregular nuclear membrane, a few hyperchromatic clumped granules, and definitely dark-stained nucleoli.

Intermediate types betwen the two above described extreme types are frequently observed in the first stage of x-ray treatment and are an indication of how x-ray acts on cancer cells. The paper does not mention frequency and appearance of mitosis.

GEMMA BARZILAI.

Sirtori, C., and Grattarola, R.: Estren Effect in Breast Cancer, Tumori **21**: 319, 1947.

Observations on the effect of estren(dioxydiethyhydrostilbene) on cancer of the breast is reported by Sirtori and Grattarola of the National Cancer Institute in Milano, and an attempt is made to explain clinical signs and symptoms following this treatment on the basis of the variation of the microscopic picture revealed in biopsies taken in sequence.

Small doses were given, 15 mmg. daily for one week followed by maintenance doses of 15 mmg. each week.

Alleviation of pain was observed, reduction in size and mobilization of the tumor itself, as well as of the axillary lymph nodes. Microscopic examination revealed no changes whatsoever in the epithelial portion of the tumor which was studied with routine staining methods as well as with such special chromosomic stains as Feulgen and acetic carmine. Instead, the connective tissue was edematous, soft, with increased size of endothelial cells and increased amount of ground substance, a finding which may well account for the mobilization of the tumor, reduction in its size, and alleviation of pain, which symptoms may mislead to the interpretation of an action of the estrogen on the tumor itself. GEMMA BARZILAI.

DeGiorgi, L.: Hydatidiform Mole. Hystopathology of the Placental Site of the Uterus, Archivio de Ostetricia e Ginecologia 52: 321, 1947.

At the Lying-in Hospital of Naples, DeGiorgi examined the placental site in four cases of simple hydatidiform mole, for which hysterectomy was performed. The operations were done 2, 19, 37, and 45 days after expulsion of the mole.

Placental site was no different from placental site in a normal pregnancy in Case 1. In the Cases 2, 3, and 4, however, a picture corresponding to Hertig's syncytial endometritis was found. Giant cells, lymphocytic infiltration, marked regressive alteration in the vessels were present. In one case, invasion of the myometrium by endometrial islands was seen, but no invasion by hyperplastic or otherwise malignant trophoblast.

Clinically, these three cases showed uterine subinvolution and stubborn bleeding. The histopathologic picture of the placental site explains those symptoms. In such cases, in spite of the pathologic nonmalignancy of the lesion, hysterectomy is the correct approach, especially after repeated and ineffective curettage. GEMMA BARZILAI.

Crossen, Robert J.: Primary Carcinoma of Bartholin's Gland, Am. J. Surg. 75: 597, 1948.

The author reports a case of carcinoma of Bartholin's gland and reviews the literature of the 88 reported primary cases. He discusses the criteria offered by several writers to identify such a primary tumor but does not offer enough details of the presented case to enable the reader to distinguish this lesion from a metastatic corpus adenocarcinoma.

The clinical characteristics of the primary Bartholin gland carcinoma, except for localization, are similar to those of other vulvar tumors. S. B. GUSBERG.

Ayre, J. Ernest: Cervical Cytology in Diagnosis of Early Cancer, J. A. M. A. 136: 513, 1948.

The detection of early cancer is always a microscopic procedure. The author proposes an annual cytologic test to detect early carcinoma. In a series of cases of about 115 women who showed cells suggestive of carcinomatous tendencies when the spatula was used, single biopsies failed to reveal any evidence of carcinoma. In those cases which did have a complete conization of the cervix and serial sections of the squamocolumnar junction, 36 preinvasive carcinomas were found and, in a still larger number, cells were found exhibiting the structure by cancer without a lesion large enough or definite enough to be labeled by the pathologist as a preinvasive carcinoma. The author concludes that the described cytologic method gives a sensitive indication of growth changes in the squamous tissues in the region of the junctional area, and it may be possible simply to scrape off a beginning area of growth in tissues, leaving no further evidence to be found in the tissue biopsy. WILLIAM BERMAN.

Gynecology

Defendi, S.: Treatment of Adnexitis by Anesthetic Infiltration of the Hypogastric Sympathetic Chain, Folia Gynecologica 43: 3, 1948.

Defendi reports 113 cases of pelvic inflammation treated by infiltration of the hypogastric chain. Acute, subacute, and chronic cases were treated. The procedure was alike

in all cases. Bed rest during the whole procedure, 5 cm. of 1 per cent solution of Novocain were injected at intervals of three to four days, the number varying from six to eight injections.

Acute and subacute cases were cured in about 50 per cent and showed amelioration in 40 per cent of the cases. Chronic cases remained unaffected.

In the acute and subacute cases, spontaneous pain was almost immediately relieved and pain on palpation disappeared after two or three injections. Local signs such as swelling of the tubes and puffiness of the cul-de-sac also disappeared after a few injections, and temperature became normal in most of the cases.

The author considers anesthetic infiltration as worth while trying in the treatment of acute and subacute lesions of the female genitals. GEMMA BARZILAI.

Menstruation

Markee, J. E.: Morphological Basis for Menstrual Bleeding, Bull. New York Acad. Med. p. 253, April, 1948.

An excellent exposition of the morphologic changes in endometrial transplants is presented with their background pattern of hormonal stimulation and their resultant liberation of forces culminating in menstrual bleeding.

The author presents a series of experimental observations in the monkey which indicate the probability that rapid regression is the first of a series of endometrial phenomena leading to menstrual bleeding. Gradual regression induced by gradual decrease in systemic estrogen levels was not accompanied by bleeding; local estrogen application could prevent rapid regression and bleeding in the face of systemic decline in estrogen levels. In all lines of observation, the bleeding phenomenon was constantly preceded by endometrial regression. This regression is thought to be dependent on withdrawal of the growth stimulus of estrogen and progesterone.

The morphologic sequence outlined is that of endometrial regression and thinning with resultant increase in coiling of the coiled arterioles. There is then marked stasis of blood in these vessels and degeneration of the peripheral endometrium; liberation of a toxin from this degenerating tissue will then cause vasoconstriction in these vessels, and weakening of vascular walls results in leakage of blood when vasodilatation ensues. The phase of vasoconstriction is pictured as one which diminishes blood loss. S. B. GUSBERG.

Miscellaneous

Valle, G.: Shape of Pelvic Brim in Northern Italian Adult Women, La Ginecologia 13: 559, 1947.

Valle examined the shape of the pelvic brim in 100 Italian women, including student nurses and housewives, in a small rural town of Northern Italy, using Thoms' technique.

According to Thoms' classification, the percentage of differently shaped pelves rated as follows: dolicopellic 6 per cent, mesatipellic 34 per cent, brachypellic 54 per cent, platypellic 6 per cent.

According to Turner's index, dolicopellic pelves amounted to 21 per cent, mesatipellic to 31 per cent, flat pelves to 48 per cent.

This small series confirms the observation that in Europe the brachypellic type prevails as compared to conditions in the United States where mesatipellic pelves are most frequently found.

Survey of American and continnental literature is given, with speculative conclusions about the influence of nutrition on pelvic architecture. GEMMA BARZILAI.

Items

The Twelfth British Congress of Obstetrics and Gynaecology

To Be Held in the Friends Meeting House, Euston Road, London, N.W. 1, July 6, 7, and 8, 1949

President: Sir Eardley Holland.
Hon. Secretaries: A. Joseph Wrigley. Ian Jackson.
58. Queen Anne Street, (Royal College of Obstetricians & Gynaecologists) London, W.1.

WEDNESDAY, JULY 6.

Morning Session. 10:00 A.M.—(Chairman: The President)

"Modern Caesarean Section." Introduced by Mr. C. McIntosh Marshall (Liverpool).

Afternoon Session. 2:00 P.M.—(Chairman: Professor Hilda Lloyd)

(1) Guest Paper, "Endometriosis." Dr. Joe Meigs (Boston, Mass.).
(2) "The Methods of Assay and Clinical Significance of Pregnanediol in the Urine." Introduced by Professor C. F. Marrian (Edinburgh) and Dr. G. I. M. Swyer (London).

8:45 P.M.—Reception by the President and Council of the Royal College of Obstetricians and Gynaecologists at the University of London, Bloomsbury, W.C.1.

THURSDAY, JULY 7.

Morning Session. 10:00 A.M.—

"Essential Hypertension in Pregnancy." Introduced by Professor George W. Pickering (London) and Professor F. J. Browne (London).

Afternoon Session. 2:00 P.M.—

(1) "The Management of Pregnancy in Diabetics." Introduced by Mr. John H. Peel (London) and Dr. G. Douglas Matthew (Edinburgh).
(2) "Hernia of Pouch of Douglas." Introduced by Mr. Charles D. Read (London).

8:00-10:30 P.M.—Reception by the President of the Congress at the Zoological Gardens by courtesy of the Council of the Zoological Society of London.

FRIDAY, JULY 8.

Morning Session. 10:00 A.M.—

"Modern Concepts in Diagnosis, Treatment, and Prognosis of Carcinoma of the Uterus."
1. "The Diagnosis by Vaginal Smear." Dr. J. E. Ayre (Montreal).
2. "Precancerous Cellular Changes in Carcinoma of the Cervix." Professor Gilbert I. Strachan (Cardiff).
3. "Prognosis Based on Biopsies." Mr. A. Glucksmann (Cambridge).
4. "The Operation of Pelvic Exenteration." Dr. Joe Meigs (Boston, Mass.).

Afternoon Session. 2:00 P.M.—

Discussion on Maternal Mortality. Introduced by Sir William Gilliatt (London).

7:45 P.M.—Congress Banquet in Guildhall

Owing to the difficulties that exist at the present time in arranging hotel accommodation, travel, etc., all those who hope to attend are requested to apply as soon as possible to Ian Jackson, M.R.C.O.G., Hon. Sec., 58. Queen Anne Street (Royal College of Obstetricians and Gynaecologists), London, W.1.

International Congress on Radiology

The Third Congress will be held in Santiago, Chile, from Nov. 11 to 17, 1949. For further information apply to the United States representative, Dr. James T. Case, 55 East Washington Street, Chicago, Ill.

American Board of Obstetrics and Gynecology

The following physicians are to be included in the list of Diplomates certified by this Board:

Bonanno, Peter Joseph, 226 Engle Street, Englewood, New Jersey, born 1909, received M.D. from Georgetown University in 1933.

Heldfond, Alfred John, 5410 Wilshire Blvd., Los Angeles, Calif., born 1911, received M.D. from University of Oregon in 1936.

Steer, Charles Melvin, Harkness Pavilion, 180 Fort Washington Avenue, New York 32, N. Y., born 1913, received M.D. from Columbia University in 1937.

PAUL TITUS, M.D.,
Secretary.

Correction

The Role of Surgery in the Treatment of Carcinoma of the Cervix

In the discussion of a paper with the above title by Dr. Frank R. Smith, published in the December issue of the JOURNAL (pages 1032, 1033), the stenographic notes included inadvertently several statements which require correction. The corrected version is as follows and should be substituted for that previously published. For purposes of continuity the entire discussion by Dr. Smith is presented.

DR. FRANK R. SMITH.—One cannot help but be impressed by the futility of using percentage figures, especially where there is any selected material, for the reason that there is the human equation involved and that differs also where we use a clinical estimation of the stage of the disease, and that is one thing surgery has done in this disease; it has shown us how wrong we have been many times in our clinical estimation of the stage of the disease.

I was interested in Dr. Taylor's estimation of operability. Various surgeons talk about operability, but this differs in different clinics. In this respect I was struck by Bonney's operability of 63 per cent as compared with Dr. Read's of 14 per cent. It would also be of interest to know how many of his patients were irradiated previous to operation and whether they should be classified as to primary operability. At Memorial Hospital in New York we have no "primary" operability; all patients are irradiated before operation.

I desire to submit the following to show the incidence of the various types of carcinoma, taking in Dr. Wm. P. Healy's regime in the first section, from 1922 to 1924. A, or Stage I, shows an increase, due perhaps to increasing publicity and better education of doctors; and B, or Stage II, shows an increase; Stage III diminishes, as would be expected, while Stage IV is about the same. In spite of improvement in material, we find pretty much of a plateau; that is, in recent years there has been a plateau in the results obtained by irradiation. For that reason, we utilized the surgical approach to this disease at Memorial Hospital, to see whether we could improve the cure rate. Now, if we take the two types Dr. Taylor so ably presented, the favorable operability, Stage I and II, and operate on them, giving them irradiation at the same time and postoperative irradiation (preliminary irradiation being given at the present time by the vaginal cone), unless we improve appreciably our over-all statistics in those two groups, the question arises as to whether we are justified in putting the patient through a major surgical procedure as a substitute for the simple insertion of the radium tandem. In other words, if our mortality is greatly increased, and if we fail to improve appreciably our five-year results, are we justified in subjecting the patient to operation?

The second group is that in which feeling of discouragement exists at present, in which we take the position that all we can do is palliate. In Stage III the salvage rate is low. In Stage IV we never have been able to do very much.

There is some justification in the courageous experiment at Memorial Hospital. Today we attempt surgery for these patients, but we must definitely ask ourselves the following questions; First, do we salvage appreciably any from a group of people who previously had no salvage? Second, do we make the patient more uncomfortable than we do with palliative irradiation? Third, is the operative mortality much greater? Fourth, what is the time of palliation?

I note that in Dr. Read's Stage III group, 22 patients, none lived eighteen months. Dr. Healy will tell you that we have had many of these advanced cases, so-called, clinically speaking, who have lived eighteen months or longer.

If we are going to evaluate this courageous experiment, we must ask ourselves these questions.

Since September 15, all patients with cancer of the cervix, whether they have been Stage I, II, III, or IV, who have entered the wards of Memorial Hospital, have been trated surgically. There have been only three cases in which exploratory operation only has been done. They had unusual complications: one had deep metastasis in the liver, which is unusual, the second had complete involvement of the iliac vessels which infiltrated these particular structures, and the third had peripancreatic disease all around the upper abdomen.

Dr. Brunschwig has objected to my term "hemitorsectomy," but I think his term of "devisceration" is just as bad. This operation which includes pelvic lymphadenectomy, removal of uterus, tubes, ovaries, vagina, bladder and rectum, with transplantation of the ureters into the colostomy loop, includes to date 16 cases with 4 deaths, or a 25 per cent over-all mortality. This mortality could be corrected to 12.5 per cent because one patient died on the ninth day after a normal convalescence and autopsy failed to show cause of death; another died of causes unrelated to the operation. But the over-all mortality is still 25 per cent.

I am not speaking critically of this "courageous experiment," and not enough time has elapsed to evaluate it properly, but unless it fulfills the qualifications I have mentioned, it is merely an example of surgical calisthenics. We should not talk about it until enough time has elapsed to evaluate properly its merits or its faults.

There is a very bad feature of this radical surgical procedure. Many aspiring surgeons stand in hero worship of a great surgeon performing these technically remarkable "all American operations." Very few hospitals, even in this city, are equipped to carry on such major surgery. These men, watching this radical procedure and getting the false impression that it is the proved and recognized treatment for carcinoma of the cervix, are going back to their hospitals and attempting to perform the operation without being able even to support the patient properly while she is on the operating table. (Blood transfusions alone often require 6 to 8 units of 500 c.c. each during the operation.)

While I feel it is dangerous teaching before enough time has elapsed to evaluate it properly, I do believe that at Memorial Hospital it is a courageous experiment, worthy of the trial because it is performed on unselected cases and the over-all figure will be an unqualified one.

Foundation Prize Award

The American Association of Obstetricians, Gynecologists and Abdominal Surgeons announces an award of $200.00 for a thesis based on original work in its field. The manuscript must be presented not later than June 1, 1949.

For further particulars apply to the Secretary, Dr. L. A. Calkins, University of Kansas Medical Center, Kansas City 3, Kansas.

CONTENTS FOR MARCH, 1949

South Atlantic Association of Obstetricians and Gynecologists Transactions of the Tenth Annual Meeting, February 12 to 14, 1948, at Augusta, Georgia

Original Communications

(Continued on page 8)

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American Journal of
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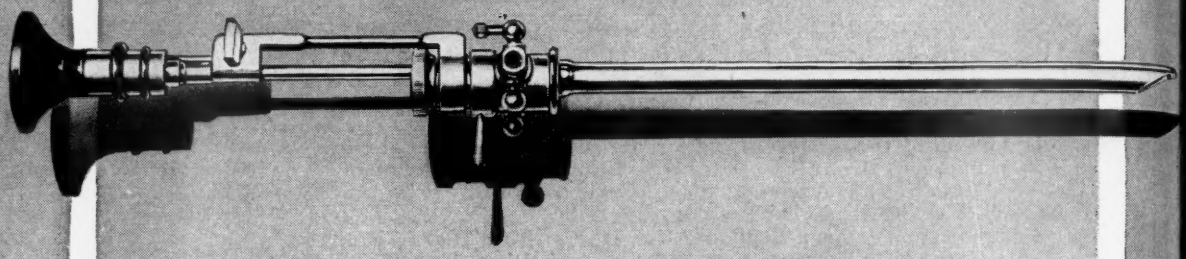
McCARTHY FOROBLIQUE PAN-ENDOSCOPE



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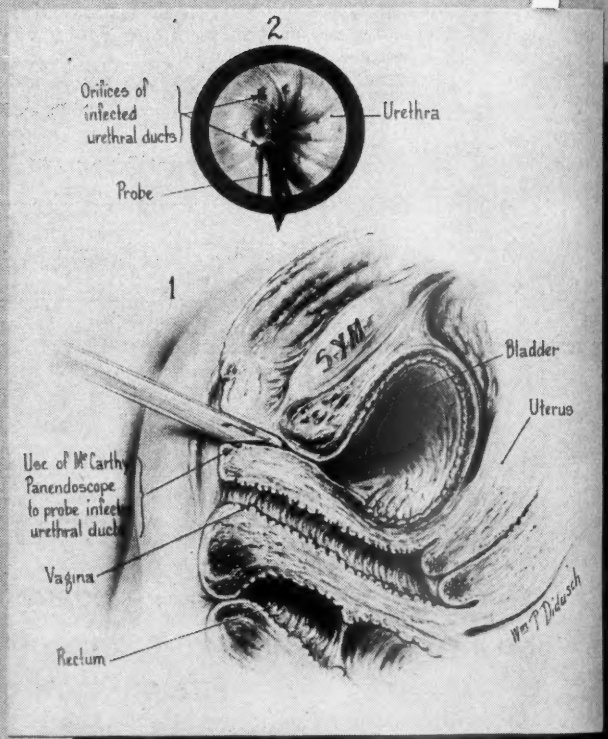

The illustration is one of a series, admirably executed by Mr. William P. Didusch, showing the technique of the Pan-endoscope. The entire series and a complete description of the instrument will be furnished upon request.

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